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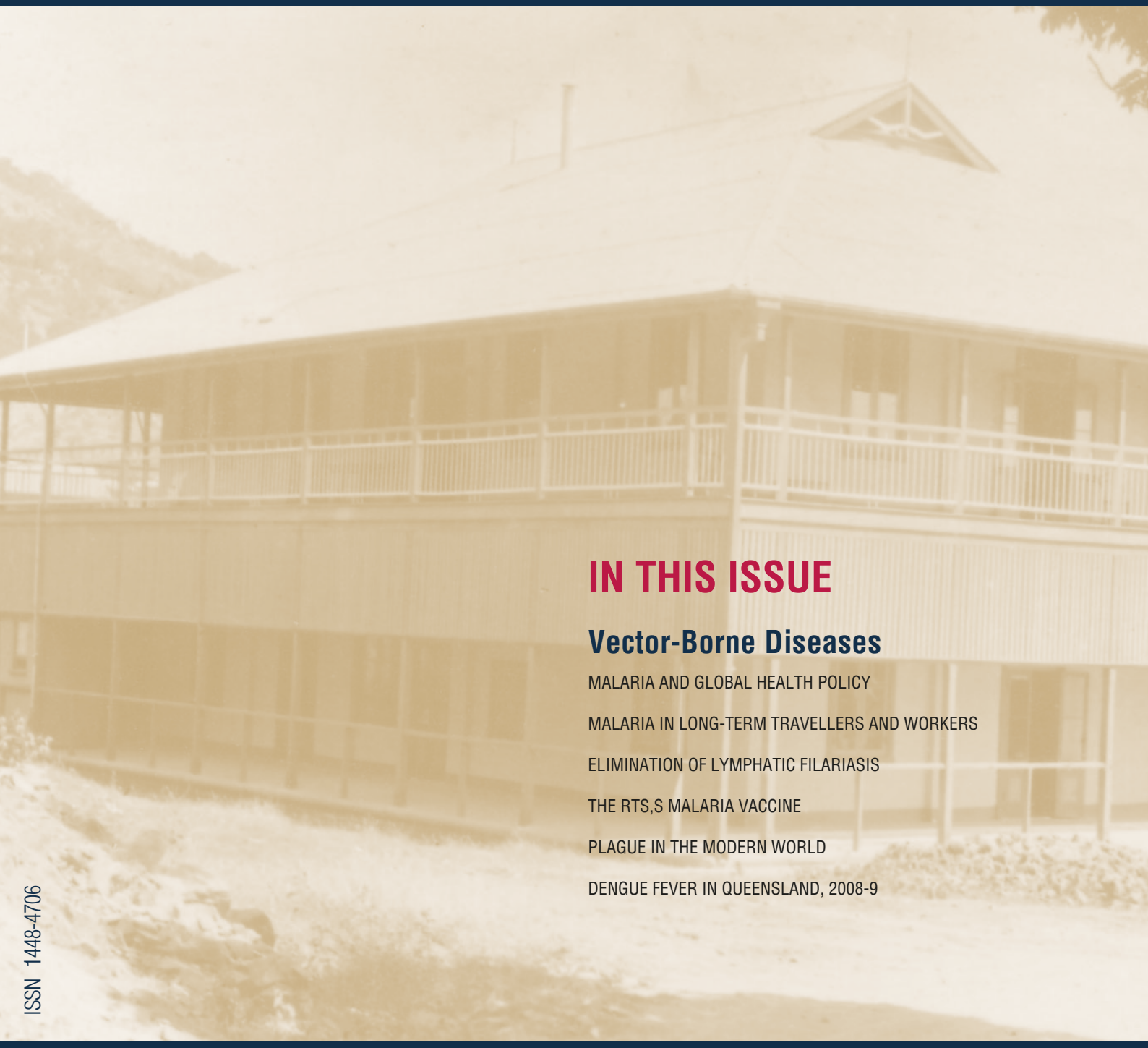

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Cover photo: The Australian Institute of Tropical Medicine in 1916 (photo courtesy of James Cook University)

EDITORIAL

VECTOR-BORNE DISEASES: MALARIA, LYMPHATIC FILARIASIS, PLAGUE AND DENGUE

Compared with what it was a decade ago, the global malaria situation has improved somewhat, with a decrease in the estimated mortality worldwide (from about a million to about 660 000 deaths per annum).[1] Improved funding for research and implementation of sustainable control measures has led to elimination (that is, no local malaria transmission in a defined geographic area) being planned or implemented in 34 malaria-endemic countries.[2,3] However, it is clear that for the foreseeable future, malaria will remain a major public health problem in many countries, particularly those in sub-Saharan Africa. Frank Ng and Peter Leggat provide a commentary on global malaria control policy in this issue.[4] If they survive for the first 5 years or so of life, residents of high-transmission regions may develop sufficient immunity to malaria to avoid severe or fatal infection and in some cases, even symptomatic malaria. Travellers, visitors and expatriate workers from non-endemic countries, however, are not thus protected and need to take malaria-prevention measures, including chemoprophylaxis. The article by Claire Woolacott in this issue[5] reviews the difficult situation of preventing malaria in long-term (>6 months) travellers and workers, the issue of self-diagnosis, and the evidence for acquisition of some degree of immunity in this population. Although the malaria parasite is an elusive immunological target, ultimately vaccines will probably be key to elimination or even eradication. The RTS,S malaria vaccine from GlaxoSmithKline is the first to reach the stage of large-scale clinical trials, and Johanna Thomson reviews the results of the trial data published to date.[6] Although clearly an imperfect vaccine, RTS,S has shown sufficient promise for GSK to announce its marketing at low cost as a public health measure. Another mosquito-borne parasitic infection is lymphatic filariasis, a very appropriate subject for an Australasian medical journal, because of the pioneering work of Joseph and Thomas Lane Bancroft in Brisbane that elucidated the transmission cycle and clinical effects of the filarial parasite in the 19th century.[7] Although lymphatic filariasis has been declared a potentially eradicable disease, and there have been substantial successes in controlling it in some areas, there are several obstacles to elimination that are described by Glenn Close in the review of the WHO's Global Programme to Eliminate Lymphatic Filariasis.[8] Plague reached Australian ports in the early stages of the third plague pandemic in the early 20th century but fortunately did not become established, unlike the situation in many other countries, where it persists or recrudesces, sometimes after many years of quiescence.[9] The article by Liana Varrone in this issue points out that worldwide, plague is still very much with us, and that changes in the epidemiology of plague, as well as other vector-borne diseases, may result from global warming.[10] Climate change may also be contributing to the expansion of the geographic reach of dengue fever, a mosquito-borne viral disease. Dengue has been introduced periodically into northern Queensland for more than 100 years, and the Cairns Base Hospital experience in the 2008-2009 dengue epidemic has been documented by Jasmine Dillon and John McBride in this issue.[11]

John Frean

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POLICY PERSPECTIVE: MALARIA AND GLOBAL HEALTH

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Abstract

The achievements of the global fight against malaria have been phenomenal. Malaria control is interwoven in the 2015 Millennium Development Goals. As 2015 is approaching, this article reviews the control of malaria over the last three-quarters of a century. Despite there having been major advances in malaria control, malaria is still endemic in 97 countries worldwide today. Continuous global effort in malaria control is still critically required. The successes and failures in battling malaria have taught us invaluable lessons, which can be applied to the fight against many other tropical diseases. The triad of technical control, global collaboration and the support of international funding organisations will be the cornerstone in handling other diseases.

Keywords: malaria, global control, elimination, Millenium Development Goals, funding

Introduction

On World Malaria Day (25th April 2014), it was declared that 'unless the world can find a way to bridge the funding gaps and endemic countries have the resources and technical support they need to implement sound malaria control plans, malaria resurgence will likely take many more lives.'[1] Such a statement is a fitting and timely call to the public health arena. Today, 97 countries have endemic malaria.[2] Half of the world's population, that is, 3.4 billion, is at risk of malaria. In 2012, the World Health Organization (WHO) estimated that there were 207 million cases, resulting in 627,000 deaths.[3] Up to 90% of these deaths occurred in Africa. Children under five years comprised of 77% of malaria deaths. In 2012, approximately 480,000 under-five children died from malaria. Sub-Saharan African countries accounted for 80% of all the world cases.[3] Malaria is endemic around the equator, in areas of the American, Asian and African continents. It is prevalent in these regions because of rainfall, warm climate and high humidity promoting breeding of mosquitoes capable of transmitting this disease. In addition, the minimum temperature threshold required for parasite development (sporogony) in the mosquito host is sustainably achieved or exceeded in these areas.

Organisations involved and strategies employed

Over the last three-quarters of a century (Table 1), there have been major advances in malaria control, led by various international organisations. Of these, WHO has been the primary orchestrating force. In 1955, WHO launched the Global Malaria Eradication Program which relied on vector control, indoor residual spraying (IRS), and systematic detection and treatment of cases.[2] Eradication was successful in many countries. However, the program was terminated in 1969, given that the goal of global elimination was proven to be unrealistic.

Today, malaria can be effectively prevented, diagnosed and treated. In primary prevention, vector control is the cornerstone. The goals are to prevent mosquito bites, and to reduce the longevity of the mosquitoes, the human-vector contact and the density of the mosquito population.[3] These are achieved with the use of long-lasting insecticidal nets (LLINs), and IRS, in which insecticides are sprayed on the walls of homes. Another primary prevention is the intermittent treatment for pregnant women in high-risk regions. Secondary prevention involves case detection with microscopy or rapid diagnostic tests, and anti-malarial therapy. Since 2011, artemisinin-based combination therapies (ACTs) have been recommended by WHO against *P. falciparum* malaria, whereas chloroquine and primaquine target *P. vivax*.[4] On World Malaria Day 2012, a new initiative was launched, known as T3: 'Test. Treat. Track.' It appeals to endemic countries to test every suspected case, to treat every confirmed case, and to track every case in a surveillance system.[5]

The Roll Back Malaria (RBM) Partnership, launched in 1998 by WHO, UNICEF, UNDP and the World Bank, is the framework to implement a coordinated global response to malaria.[6] More than 500 partners work together to optimise use of scarce resources, avoiding fragmentation and duplication. RBM's strategy aims to reach universal coverage and strengthen health systems through the Global Malaria Action Plan (GMAP).[4] The GMAP comprises of three strategic components: control, elimination and research. WHO defines control as 'reducing the disease burden to a level at which it is no longer a public health problem.'[7] This involves firstly, the scaling-up of preventive and therapeutic interventions at national level; and secondly, sustaining control over time. Elimination is the 'interruption of local mosquito-borne malaria transmission in a defined region, although imported cases will continue to occur.'[7] At present, 7 of the 97 endemic countries are in the elimination phase.[3] Furthermore, research into new approaches will sustain malarial control and elimination efforts.[4] Practically, RBM assists at all levels in advocacy, policy and regulatory support, financing, supply chain management, communication and behaviour change methodologies, monitoring and evaluation, and preparation and support for crises.[4]

The Global Fund is a financing institution that provides funding to countries to prevent, treat and care for people with HIV/AIDS, tuberculosis and malaria. It distributes 60% of the total international funding in fighting malaria.[8] This financing has enabled endemic countries to increase access to LLINs; the proportion of households owning LLINs in sub-Saharan Africa has risen from 3% in 2000 to 54% in 2013, while the percentage protected by IRS increased from under 5% in 2005 to 36% in 2013.[3] There have been more than 310 million LLINs distributed and 260 million cases of malaria treated through the Global Fund.[8]

The Global Fund investments have orchestrated expansion of the coverage of ACTs in many countries where drugs resistance is high. Through the Affordable Medicines Facility – Malaria program, countries can increase the provision of affordable ACTs through the public, private and NGO sectors. The Global Fund has negotiated with drug manufacturers to reduce the price of ACTs, and to require the same sales prices for both public and private sector purchasers. It pays most of this reduced price (a 'buyer co-payment') directly to manufacturers. This lowers ACTs costs to the first-line buyers and subsequently to the patients. The prices of ACTs will be lower than the monotherapy price, thus, discouraging monotherapy use and lowering resistance risk.[8]

The Malaria Atlas Program (MAP),[9] founded in 2005, employs spatial medical intelligence in the effective planning of global malaria control. Teams of geographers, epidemiologists, statisticians, public health physicians, and biologists are involved. It maintains a spatial database on the measure of malaria endemicity (known as the parasite prevalence rate),[9] based on medical intelligence, satellite-derived climate data and community-based estimates of prevalence.[10] It provides the basis for morbidity, mortality and co-infection burden estimates, which ultimately aid resource allocation.[8] In 2012, the proportion of malaria cases detected by surveillance systems was close to 14% of the total estimated burden.[3]

Malaria and the Millennium Development Goals

Malaria control is interwoven in the Millennium Development Goals (MDG).[11] The eight MDG Goals are a set of agreed objectives by all the world's countries and leading development institutions, to address various pressing needs of the world's poorest by 2015 (Table 2). Malaria control is the main focus in Goal 6C – to have halted by 2015, and begun to reverse, the incidence of malaria.[11] Since 2000, malaria mortality and illnesses have fallen significantly, with over 1.1 million lives saved.[6] Mortality rates in Africa have decreased by one-third. 168 million at-risks individuals were protected by IRS. LLINs have reduced malaria incidence by half in children

and reduced mortality by 20%.[5] Fifty-two countries are on track to reduce malaria incidence rates by 75% by 2015.[3]

Malaria control supports MDG4 (to reduce child mortality), as malaria accounted for 7.3% of global child deaths in 2012.[3] To achieve this, WHO recommended that all children aged 3-59 months be given malaria chemoprophylaxis through regular immunisation services at defined intervals.[5]

Malaria control impacts on MDG5 (to improve maternal health). As pregnancy increases the incidence of malarial complications, WHO recommends intermittent preventive treatment (IPT) for all pregnant women at each scheduled antenatal visit in areas of moderate to high malaria transmission. The uptake rate of this IPT program amongst the at-risk countries averaged at 37% in 2012 across the world.[3]

Furthermore, malaria control reflects MDG8 – global partnerships for development and access to affordable drugs. In 2013, the Global Fund announced a target of raising US$15 billion for the next 3 years, with the aim to achieve a universal coverage of LLINs and access to treatment. An additional 200,000 lives could be saved every year with this resource. This funding model also targets specific populations including women, sex workers, intravenous drug users, homosexual men, prisoners and migrants.[8]

Malaria control has been shown to reinforce the capacity of health systems. This occurs in the forms of supporting delivery capacity, malaria epidemiological surveillance, monitoring and evaluation.[12]

Lessons learned from the efforts in dealing with malaria

Several important lessons have been learned from the fight against malaria. The first major program, namely the Global Malaria Eradication Program, was successful in eliminating malaria in Europe, North America, the Caribbean, South-Central America, and parts of Asia. Success in controlling malaria has been attributed predominantly to the use of LLINs, IRS and effective medication to treat cases and interrupt transmission. However, there was minimal success in sub-Saharan Africa, where most malaria cases occur. The termination of the program was due to technical challenges of executing the strategy, especially in Africa.[13] Logistics, financial and geographical barrier remain a challenge in the tropics. The countries in which limited progress is made with malaria control are commonly those where political instability, war, or poverty have hindered effective implementation of these interventions.[14] As such, the termination of the program demonstrated that a universal approach is ineffective, and each country pursuing elimination needs to assess its situation and develop strategies that match its individual needs.[2]

To date, malaria control has demonstrated obvious success through collaborations. The RBM partnership's GMAP exemplified the importance of agreement among all partners around the goals, strategies, and activities that the partnership pursues. Success is also the result of the prioritisation of resources and consolidating the alignment across various initiatives in each affected country.[4] Collaboration has many benefits, which enhances political support, global awareness, learning from each other's successes and difficulties, and alignment of control and prevention strategies.[2]

From history, one notes that malaria attracts such attention not only because it causes significant morbidity and mortality globally, but also because it is linked to the MDG. As a result, there is an increased awareness and advocacy in the countries affected by malaria and subsequent funding to combat the disease.

The MAP was successful in developing an atlas to demonstrate regions affected by malaria. It was shown that a spatially progressive elimination strategy (known as 'shrinking the malaria map') has encouraged many countries to take up the elimination challenge as their neighbours have joined the effort.[2] However, it has been argued that addressing the 'easy-to-eliminate' settings in the map edges only brings marginal benefits to such areas, at the expense of those where the burden of malaria is highest. A synchronised global effort, which is locally adapted in various settings, is needed.[13]

Despite the existence of MAP, tracking progress in malaria control remains difficult. The current surveillance systems detect only about 10% of the global cases. There is an urgent need to improve surveillance systems to ensure an effective malaria response in endemic regions.[5]

In summary, history reveals that conquering malaria will require multi-factorial interventions, including political, social, financial, technical as well as operational dimensions. Other sectors including education, defence, environment, industry, and tourism, also need to be enlisted to ensure ultimate success.[5] The priority to control malaria needs to be incorporated into the development agenda in all affected countries.

Application of the lessons learned to other health problems

The lessons learned from malaria control can be applied to other diseases and health issues. Firstly, global collaboration is crucial in fighting against any major infectious diseases, as only in doing so, will it generate enough global awareness, technical support, political awareness and international funding to achieve adequate coverage and to develop control strategies. This is seen in WHO's fight against the neglected tropical diseases. Those targeted for global eradication are dracunculiasis (guinea worm disease) in 2015 and yaws in 2020.[15] Secondly, each affected country needs to develop its own strategies and programs, while liaising with other endemic regions. A blanket universal approach will be ineffective, as seen in the Global Malaria Eradication Program. Thirdly, development of an international fundraising organisation will be greatly beneficial to fight any health issues, as exemplified in the case of the Global Funds in malaria, tuberculosis and HIV/AIDS control. The strategy employed by Affordable Medicines Facility – Malaria program can be used in dealing with other diseases, proving that through providing subsidy to the manufacturer, the price of vital treatment can be kept low and affordable. Another successful funding organisation example is the Bill and Melinda Gates Foundation campaign against tuberculosis. Fourthly, in the technical aspects of malaria control, the use of long-lasting insecticidal nets and indoor residual spraying can be applied or suitably adapted on a larger scale against various vector-borne diseases across the tropics, such as lymphatic filariasis, Chagas' disease, yellow fever, Japanese encephalitis, and dengue fever.[16] Fifthly, the MAP strategy can be applied to other infectious diseases. Specifying pathogens' prevalence and endemic mapping would help to monitor progress and to provide information for funding allocation, with the ultimate goal of containing and eliminating the diseases.

Conclusions

The global fight against malaria has been phenomenal. Under the leadership of WHO, global collaboration has contributed significantly to reducing malaria-related morbidity and morbidity through the use of long-lasting insecticidal nets, indoor residual spraying, and systematic detection and treatment of cases. Despite such efforts, the fifty-two countries that are on track to reduce their malaria case incidence by 75% by 2015 only account for 4% (or 7 million) of the global estimated cases. There are still the unconquered 14 countries which account for 80% of malaria deaths.[5] Continuous global effort in malaria control is still critically required. In a broader context, the successes and failures in battling with malaria over the last century have taught us invaluable lessons that can be applied to the fight against many other tropical diseases. The triad of technical control, global collaboration and the support of international funding organisations will be the cornerstone in handling any other major diseases of public health importance.

Table 1. Timeline of malaria control, 1940s to 2000s

1940s	Chloroquine discovered 1934 and used as antimalarial in 1946 DDT insecticidal properties discovered in 1939
1950s	World Health Assembly 1955 announces WHO Eradication Program Widespread use of DDT and chloroquine Resistance reported to DDT
1960s	Resistance reported to chloroquine WHO Malaria Eradication Program abandoned in 1969
1970s	Resurgence of malaria
1980s	Insecticide-treated bed nets trialled by WHO
1990s	Artemisinin-based combination therapies emerge in late 1990s Roll Back Malaria Program launched in 1998
2000s	MDGs launched; Goal 6C focuses on halting and reducing malaria

Table 2. Millennium Development Goals[11]

Goal 1	Eradicate extreme poverty and hunger	By 2015 halve the proportion of people living on less than $1 per day
Goal 2	Achieve universal primary education	Ensure that by 2015 children everywhere, boys and girls alike are able to complete a full course of primary schooling.
Goal 2	Promote gender equality and empower women	Eliminate gender disparity in primary, secondary, and tertiary education by 2015
Goal 4	Reduce child mortality	By 2015 reduce the under-five mortality rate by two-thirds.
Goal 5	Improve maternal health	By 2015 reduce the maternal mortality rate by three-quarters.
Goal 6	Combat HIV/AIDS, malaria and other diseases	By 2015 have halted and begun to reverse the spread of HIV/AIDS and reverse the incidence of malaria and other major diseases.
Goal 7	Ensure environmental sustainability	By 2015 halve the proportion of people without sustainable access to safe drinking water and basic sanitation; integrate the principles of sustainable development into country policies and programs.
Goal 8	Global partnership for development	By 2015, in cooperation with pharmaceutical companies, provide access to affordable essential drugs in developing countries.

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MALARIA INFECTION IN LONG-TERM TRAVELLERS AND WORKERS IN MALARIA-ENDEMIC REGIONS

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Abstract

Objective: to describe the risk of malaria infection in long-term overseas travellers and workers in malaria-endemic regions, identifying risk factors and prevention management, and to briefly examine the possibility of non-immune travellers acquiring immunity.

Methods: The literature search was limited to relevant open-access articles, written in English, from the year 2000 until May 2013. Pubmed, the Cochrane Library, Google Scholar and the Malaria Journal were searched.

Results: There are increasing data that suggest long-term travellers are at higher risk of malaria infection, through cumulative exposure, and non-compliance with or failure of protective measures. Atovaquone/proguanil and doxycycline are best tolerated for chemoprophylaxis, but no regimen offers guaranteed protection or is without adverse effects. Non-immune travellers have been shown to develop specific antibodies for malaria strains, and after 12-24 months, their immune systems may adapt to regulate their inflammatory response, providing protection from severe clinical disease, but evidence is not conclusive, or completely transferable to long-term travellers.

Conclusion: Current evidence illustrates the need for standardised recommendations for long-term travellers, which also allow for consideration of individual needs. The immune response in non-immune travellers needs further research, and can contribute to knowledge that will assist with vaccine development.

Keywords: malaria, long-term travellers, prevention, acquired immunity

Background

Malaria is the most important infectious parasitic disease threat globally, currently causing an estimated 660 000 deaths per year,[1] and is both treatable and preventable.[2-4] Despite global efforts to control and eradicate malaria, it persists and causes not only public health risks, but impacts the social and economic sectors of countries affected.[5] Most transmission occurs in the tropical and sub-tropical regions of the world with seasonal variances,[4,6] though it is not an exclusively tropical disease.[2,5,7] Populations residing within malaria-endemic regions acquire protective immunity to the specific strains of the parasite found locally, reducing clinical disease and the risk of mortality.[2,5,8] The increasing overseas travel to these regions for work and leisure, places non-immune travellers at high risk of infection.[5,6,8] Vaccines for malaria have remained elusive, and at this stage no definitive protection exists for residents or travellers in endemic regions.[2,4,9] Prevention of malaria partly depends on avoiding exposure to the parasite vector, the female *Anopheles* mosquito.[2-4] Chemoprophylaxis and bite-prevention methods are the standard protection tools for travellers, and non-compliance to these has shown to increase infection rates.[6,11] The emphasis of research and travel guidance has been on short-term travellers, and the consequences of longer-term exposure in malaria-endemic regions has only recently been broached.[12] Long-term overseas travellers and workers in endemic regions, who are commonly in the defense force, health care, or voluntary roles, may endure cumulative exposure to the parasite, cease chemoprophylaxis regimens, and become apathetic towards compliance of personal protective measures, increasing their risk of infection further than short-term travellers.[7,12,13] The immunological mechanisms for acquiring immunity to malaria are not well understood, but there are suggestions that a non-immune adult may develop a level of protection from severe malaria, if they remained in a malaria-endemic region for a prolonged period of time.[5,8,14] This discussion will focus on reasons for non-compliance in long-term travellers, effective prevention management for travellers who remain in malaria-endemic regions for more than 6 months, and address the suggestion of non-immune individuals acquiring immunity during their period of exposure.

The searched literature defines 'long-term' as being more than a 6-month period;[12,15,16] for consistency, this discussion will use the same definition, and the term 'long-term traveller' will be used broadly to include all individuals who for any reason, whether paid work, voluntary work or leisure, reside in any malaria-endemic region for more than 6 months consistently, and have never lived previously in a malaria-endemic area, being therefore considered 'non-immune'. Bite prevention by using vector-barrier protection, has been proven through previous studies to be an important and effective method to decrease or prevent the risk of infection.[2,4,6,17] Methods include window and door screening, personal insect repellents, residual indoor insecticide spraying, insecticide vaporisation, insecticide-impregnated bed nets, reducing skin exposure with appropriate clothing, and remaining indoors during peak mosquito-feeding times.[18,19] Chemoprophylaxis is frequently recommended as protection from infection, on the basis that personal barriers may fail to prevent exposure. Several international guidelines are available for travellers that discuss the various methods and regimens.[12,17,18,20] However, all have potential adverse effects, and no chemoprophylaxis guarantees prevention of malaria infection, even when adequately administered.[3,12,15]

Methods

A literature search was carried out in Pubmed, the Cochrane library and Google Scholar, and the Malaria Journal. Search terms 'Immunity', 'non-immune workers/travellers', 'volunteer workers', 'travellers', 'long-term workers/travellers', and 'acquired immunity', 'cell-mediated immunity' alternatively combined with the key word 'malaria'.

Limitations

Articles accessed were free of monetary cost and registration, were available in the English language, published after the year 2000, with any study design. The search aimed for studies with non-immune participants in malaria-endemic regions for a minimum period of 6 months; however, due to the limited available material, literature that is outside of these criteria was referred to, in order to assist with drawing conclusions about issues with insubstantial evidence. Most studies observed non-immune soldiers or health workers, which may cause sample bias as these groups tend to be well-informed about health issues, generally have the necessary barrier protection and chemoprophylaxis provided for them, and have medical treatment of potential infections available.[15] However, malaria infection and non-compliance with prevention regimens have been shown to occur in these groups, so extrapolation from these studies to non-immune travellers is possible. These two groups are also easier to monitor, to enroll in studies, and have large sample populations available in single locations, making them convenient study groups compared with independent long-term workers and travellers.[15] Literature will be appraised according to the National Health and Medicine Research Council evidence hierarchy.[21]

Results

Malaria infection and non-compliance in long-term travellers

An estimated 30 000 non-immune travellers are infected with malaria each year, with an average 500 cases within Australia,[22] though a portion of these are immigrants from endemic-regions.[11,15] Most studies describing long-term travellers are cross-sectional surveys or cohorts, which observe and assess the behaviors and habits associated with malaria prophylaxis, often using the military for convenience and large sample sizes. Experimental studies are difficult to carry out in this setting, due to the very need for compliance with the intervention being studied, given that non-compliance of the travellers is the reason for study in the first place. They contain various biases including volunteer and information bias, and despite the large cohorts recruited, are a weaker form of evidence, according to the NHMRC.[21] However, results of these studies are consistent, and recent literature agrees that the risk of malaria infection correlates with the time spent in high-transmission regions, and therefore long-term workers are at more risk of developing malaria than short-term travellers.[12,16] Authors give two reasons for this; the first being that more time spent in a malaria-endemic area provides more potential contact with the vector, leading to repeated transmission of parasites, increasing parasite density in the blood, and the higher likelihood of clinical illness.[5,7,16] The second, and more commonly stated reason, is that non-compliance to all prevention measures more frequently occurs in long-term travellers.[10,12,23] The reasons for non-compliance ultimately come down to an individual's experience, knowledge base and expectations. Often, the longer an individual lives in a region, the more comfortable he/she becomes with the associated risks, and preventive measures lapse.[7,10,15,16] There is a lack of knowledge regarding long-term administration of chemoprophylactic medication, with known short-term adverse effects from all combinations of drugs, and limited evidence that they are either safe or unsafe for long-term use, which causes some travellers to stop taking them.[10,12,24] Therefore chemoprophylaxis is ultimately determined by personal preference regarding daily or weekly regimes, personal adverse reactions, availability of drug, and perhaps in the case of occupational travellers, what the company provides.[12] Determining the quality of medication, or identifying a counterfeit drug, can be difficult in some countries, and while many short-term travellers will buy their drugs from their home country, long-term travellers may not be able to access additional drugs from a trusted source, leading them to cease taking chemoprophylaxis altogether.[12,15,25] A cross-sectional survey of anti-malarials in southeast Asia in 2004, showed alarming results, with 53% of 'artesunate'-labelled drugs not containing any artesunate, and 9% of mefloquine tablets containing less active ingredient than stated on the package.[25] Counterfeit drugs are therefore a real concern for travellers, as well as being a significant public health issue in those countries affected, and can be responsible for inadequate chemoprophylaxis and treatment of malaria.

Malaria prevention and management for long-term travellers

At this stage no perfect standard chemoprophylaxis regimen has been found for long-term travellers.[12,15,16] This is due to the individual nature of a person's itinerary, compliance behaviors, medical history, personal preference, and adverse reactions to antimalarials. In order to effectively manage malaria prevention in long-term travellers, preparation should include consultation with a medical travel specialist, education for the traveler about malaria vector behavior, transmission patterns and risk of infection for the intended travel location, resistance or tolerance to antimalarials for the region, malaria symptoms, treatment options, available health services where they will be traveling, and potentially include diagnostic self-test kits and treatment options if isolated from medical help.[18] Prevention through both personal barrier protection and chemoprophylaxis should be emphasized; however, as the risk of malaria increases for long-term travellers,[5,12,16] the World Health Organization (WHO) has produced a stand-by emergency treatment (SBET) guide for travellers who have symptoms, to self-treat with antimalarials when medical care is more than 24 hours away.[15] Research is lacking as to the efficacy of SBET for independent travellers at this stage, and requires further education for the traveller in order to be used appropriately.

Long-term travellers require a chemoprophylaxis regimen that offers the best chance of compliance over a prolonged period. Jacquerioz's systematic review concluded that proguanil-atovaquone and doxycycline regimens ultimately led to better compliance in regions with choroquine-resistant *Plasmodium falciparum*.[11] A randomized trial by Schlagenhauf in 2003 drew a similar conclusion,[26] indicating that these may be the better antimalarial choices for long-term travellers, but results are inconclusive for the most effective drug for malaria prevention,[11] and changes in parasite susceptibility to chemoprophylaxis alters the effectiveness of drugs.[27] The Australian Defence Force often provides doxycycline to officers deployed to malaria-endemic regions, as it also provides protection from other tropical diseases they may encounter such as leptospirosis and rickettsial infections, which could also be a consideration for some independent travellers.[13] Regimens could be seasonal according to the region of travel and transmission patterns, allowing travellers to take antimalarials only when there is an increased risk of infection, and cease administration when the risk lessens.[12,15,16]

The safety of long-term chemoprophylaxis has not been adequately determined, due to a lack of research and field studies.[18] However, given the ongoing and increasing risk of travellers contracting malaria with length of stay, organizations such as the Centers for Disease Control and Prevention (CDC) and Public Health England (PHE) recommend that chemoprophylaxis continues according to each medication regimen, for as long as a person remains within high-risk areas,[18-20] along with bite-prevention measures. At this stage, there is little evidence to suggest concerns with long-term use additional to the adverse effects already established for short-term travellers, apart from possible retinal toxicity caused by the cumulative use of chloroquine, which may occur after 5 years of use.[18-20] Doxycycline has been used safely by the military as a long-term antimalarial and has no recommended limits to length of use, with the advantage of protecting the person from other infectious diseases.[19,20] Mefloquine has also been used safely long-term, (notwithstanding concerns about neurotoxicity) and may encourage compliance due to the weekly dose regimen, as opposed to antimalarials that require a daily dose, though compliance for both daily and weekly regimens have been shown to decrease with long-term use.[18]

Self-diagnosis kits

The gold standard method for diagnosis is blood smear microscopy, which identifies the malaria parasites;[2,3,6] however, this requires expertise and adequate resources, leaving much diagnosis in poorer regions to clinical judgment and rapid diagnostic tests (RDT) with varying sensitivity and specificity, and none of which are completely reliable. However more recent developments with RDTs are showing potential for them to be an important diagnosis and management method in resource-poor regions.[28-30] Travellers who carry RDTs for their own use should be aware of their limitations, especially in hot and humid temperatures that may affect results.[15,28] There are over 200 rapid diagnostic tests manufactured for malaria, which are generally targeted at *P. falciparum* or *P. vivax.* The WHO has developed standardized performance testing of over 128 of these since 2008, which includes tests for stability, ease of use and cost; however, there is no indication as to suitability as self-tests for lay travellers, as opposed to healthcare workers.[28] A study at a health clinic in Mombasa, Kenya, observed 98 febrile patients carry out their own dipstick tests, using the ICT Malaria Pf test, which targets the histidine-rich protein 2 (HRP-2) of *P. falciparum*, and is advertised as being a travellers' self-diagnostic test.[29] The results showed that while the test had a sensitivity of 92.5% and specificity of 98.3%, one-third of the patients were unable to use the test properly to obtain a result. The most common reasons for this were being unable to draw blood via a skin prick, and being unable to identify and interpret results. None of the participants had used the test before and only had access to the manufacturer's manual, illustrating the importance of education prior to travel in order for people to carry out these tests themselves correctly, especially under conditions of illness that increase stress, and can affect their ability to carry out the test correctly. However, Rennie *et al* (2004) found that education prior to use improved but did not guarantee correct application and interpretation of results of RDTs.[31] A significant problem observed with RDTs, and even microscopy, is false-negative results when there is a low parasitaemia level, usually below

5 000/µl, but this threshold level can change according to device stability in changing environments, such as increased humidity.[15,29,30] This may be a problem for non-immune travellers, as a low parasitaemia density can still lead to severe disease and morbidity.[3]

Potential for acquiring immunity

Understanding the process of acquired immunity is considered important in the development of a malaria vaccine.[2,5,8,14,24] In terms of this discussion, immunity is not the traditional concept of the bodies' ability to completely remove a foreign biological threat, with no clinical illness observed in the person. Rather, it is the adaptation of the immune system to recognize and resist malaria parasites, reducing severity of clinical disease, without completely curing the body of the parasites.[4,5,8,32] Children are at the greatest risk of severe infection in endemic regions, which is reflected in mortality rates, as their immune systems are still developing.[4,5,32] The length of time needed to gain protection from clinical malaria illness has been suggested at 10-20 years of exposure, requiring an average of 5-10 infective bites per year, and continues over a lifetime.[5,17]

Rate and strength of immunity development is also thought to be influenced by the intensity of malaria transmission,[9] and communities with lower transmission rates or seasonal transmission, can experience high morbidity and mortality during a new epidemic.[5] The exact mechanisms that initiate naturally acquired immunity to malaria remains uncertain,[5] although numerous studies have attempted to isolate pathways and key cellular processes.[8,24,32] Individuals are considered immune when they carry a level of parasitaemia in their blood but do not manifest a fever.[5,14] It is suggested that this immunity wanes once exposure to the parasite ceases for a period of time, such as when people emigrate, or move away from the transmission area,[5] but no conclusive documentation has been found regarding this process.[3,11,33] Most of the immunological studies are based on mice or in-vitro models, which while considered to be relatable to humans, have not brought forward conclusive or consistent evidence to illustrate precise response pathways.[14,32,34]

The review by Doolan *et al* (2009), has limited value in this respect as it focuses on less-complicated infections in chronically-exposed communities; however, it does suggest that non-immune adults may be at higher risk of severe disease and mortality from an acute attack, compared to exposed children younger than 5 years at their most vulnerable state, even with malaria at low parasitaemic densities.[5] This is possibly due to the rapid pro-inflammatory state of an adult's advanced immune system through cross-reactively primed T cells, which develop over a lifetime of environmental exposures. A pro-inflammatory response releases inflammatory cytokines which have cytotoxic effects on both the human body, is not targeted enough to cure the disease, and instead worsens pathology and severity of illness.[14,34] In a state of 'immunity', there is a balance of pro-inflammatory mediators to destroy and clear the parasite, and anti-inflammatory mediators, to down-regulate the detrimental inflammatory response, and lessen clinical manifestations until they are absent.[14] Some studies observed the transmigration of people considered non-immune into high transmission areas of *P. falciparum*, and showed that while initially all age groups were affected equally by clinical disease, after 12-24 months, within which there were 4-5 exposures to infection, adults appeared to carry an immunity similar to life-long residents from the area, and develop anti-parasitic immunity more rapidly than children.[5,14]

There is a suggestion that a traveller that can produce a specific antibody response against a strain of malaria may have a reduction in severity of clinical illness,[8,32] and several studies have identified that a proportion of non-immune travellers develops these antibodies, though their importance in reducing infection remains unclear.[8,14,35] It is known that malaria-specific antibodies inhibit cytoadherence, erythrocyte invasion, and the parasite's cellular processes.[14,34] It is also believed that initial immunity to severe malaria and mortality is rapid, perhaps even occurring after the first infection,[5,34] though these findings are not consistent across all studies,[36] but the hope would be that while long-term travellers may still experience the febrile illness, their risk of death could be greatly reduced. However, once again, this process is not understood, nor does there appear to be a way to induce this initial immunity prior to travel, though vaccine trials continue. The use of low-dose antimalarials to suppress clinical disease while enhancing the development of acquired immunity[37] is an area of research which has relevance, but is beyond the scope of this discussion.

Conclusion

Non-immune travellers who remain in malaria-endemic regions for more than 6 months are at higher risk of malaria morbidity and mortality. This is due to cumulative exposure to the infection and non-compliance or failure of preventive measures, including barrier-protection from the mosquito vectors and chemoprophylaxis using antimalarial drugs. There are many reasons for non-compliance that have been briefly addressed, and preventive regimens need to be individually tailored to future long-term travellers to ensure their appropriateness for the person, and to increase likelihood of compliance for a prolonged period of time. Despite the promising findings of specific antibody production and evidence of acquiring immunity, mechanisms behind these immunity changes are still not fully understood, and there is little conclusive evidence to suggest that all long-term visitors are able to develop their own immunity to severe illness; therefore prophylactic measures remain critical in all non-immune travellers irrespective of the length of their trip. Acquiring immunity to malaria is an area of study that is associated with the development of vaccines, and will likely receive more attention as more non-immune workers remain in these regions for longer periods of time. Most research currently focuses on children due to their high mortality rates within malaria-endemic regions, which may not correlate to the adult long-term traveller. The quality of evidence is generally weak across this discussion, with the exception of some comprehensive reviews, but more research is needed for long-term travellers and malaria exposure.

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ELIMINATION OF LYMPHATIC FILARIASIS: TIME TO THINK LOCALLY AND ACT GLOBALLY

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Abstract

Lymphatic filariasis (LF) is caused by vector-borne, tissue-dwelling nematodes (filariae). It is responsible for acute and chronic morbidity encompassing limb lymphoedema and urogenital disease. Estimates suggest there are almost 1.4 billion people at risk of LF in 73 endemic countries. There have been remarkable successes in large scale LF elimination, notably in Asia and in developed countries (tropical USA and Australia). The WHO launched the Global Programme to Eliminate Lymphatic Filariasis (GPELF) in 2000. The rationale for GPELF is that vector transmission and worm reproduction thresholds exist that can be changed by mass drug administration (MDA). Experience with MDA, vector control and other strategies (sanitation, economic development) suggests that, although MDA has been successful (in some localities) in meeting theoretical targets for reduction of microfilariae levels, sustainable change in transmission can take longer than projected, and requires significant local and/or regional expertise and resources. Elimination of LF, at least in localities with certain environmental, vector and socioeconomic features, is likely to fail without more innovative local and regional programs in a global strategic context.

Keywords: lymphatic filariasis, elimination strategies, mass drug administration, vector control, GPELF

Background

Lymphatic filariasis (LF) is caused by vector-borne, tissue-dwelling nematodes (filariae). Most human LF infections are caused by *Wuchereria bancrofti* and the remainder by *Brugia malayi* and *B. timori*;[1] different filarial species cause onchocerciasis and loiasis.[1] The transmission cycle involves humans with microfilariae (MF) in the blood that infect the insect vectors, comprising various species of haematophagous mosquitoes (Fig.1).

Although most infected individuals do not exhibit symptoms, many have lymphatic damage and there is a significant morbidity due to LF, ranging from acute inflammation to limb lymphoedema (elephantiasis) and genital disease (hydrocoele, chylocoele).[1] Estimates suggest there are 1.4 billion people at risk for LF in 73 endemic countries.[1]

The World Health Organization (WHO) added LF to its list of 'eradicable' diseases when success with smallpox provoked enthusiasm for disease eradication. Availability of new, rapid diagnostic tests and evidence for the efficacy of single dose treatment made population level mass drug administration (MDA) feasible.[2] The WHO declared LF eradicable in 1997 and launched the Global Program to Eliminate Lymphatic Filariasis (GPELF) in 2000.[3]

Elimination of infection requires regional interruption of transmission and cessation of new infection, and ongoing control measures may be required.[4] Eradication implies worldwide interruption of transmission, with intervention no longer required, as with smallpox.[5] Terminology is loose and the GPELF rhetoric implies eradication (at least as a 'public health problem') but it is based on national elimination.

The GPELF has the twin aims of interrupting transmission by mass treatment of populations (reducing MF rates to unsustainable levels) and reducing morbidity, although the latter is not consistently addressed.[5] From 2000-2010 about 3.4 billion treatments were delivered to more than 900 million people in 53 countries.[6]

Elimination of lymphatic filariasis is theoretically feasible. There are no animal reservoirs for bancroftian filariasis and no epidemiologic overlap between human and non-human hosts for *Brugia malayi* infection.[7] The GPELF intervention priorities are logically anchored in assumptions about parasite transmission (i.e., there is a threshold of MF density below which transmission is not sustainable) and the capacity of MDA to achieve that threshold.

The objectives of this contribution were to review the published literature on the assumptions underpinning GPELF and its implementation, and to identify predictors and likelihood of success in local elimination of lymphatic filariasis.

Search strategy and methods

A PubMed search was carried out using the terms 'lymphatic filariasis elimination' or 'GPELF' and 'lymphatic filariasis and MDA'. The search was restricted to review or systematic review articles published in English, 2008–2013. In addition, specific searches were included for 'DEC and filariasis', 'ivermectin and lymphatic filariasis' and 'albendazole and lymphatic filariasis'. Articles were selected on the basis of relevance and additive information. References in selected papers were reviewed and additional relevant papers found. WHO sources and the Cochrane Library (2 reviews found) were also searched. Selected references are used in this article. A full list is available on request from the author.

Results

Mass drug administration

The GPELF target is for at least 65% of people (80% in the Pacific program and in some reports elsewhere) to receive annual albendazole (ALB) with either diethylcarbamazine (DEC), or ivermectin (IVM) where onchocerciasis is also endemic.[8] The lifespan of *W. bancrofti* is said to be 5-6 years, so GPELF predicts that 4-6 rounds of annual MDA will reduce microfilaraemia to unsustainable levels (assumed to be less than 1%).[3] The timing has rarely, if ever, proved correct in practice, even in successful programs. There is also evidence that as host MF density decreases, *W. bancrofti* longevity may increase,[8] calling into question the required time scale for MDA.

DEC is the mainstay of LF MDA, but although it has been in use for 60 years its mechanism of action remains unclear.[3] It reduces circulating MF and kills a proportion of adult worms.[9] A key stimulus for GPELF was the acceptance of the efficacy of a single annual dose of DEC rather the traditional 12-14 days. The value of single-dose DEC has since been confirmed, although only in observational studies and clinical trials comparing DEC to DEC combined with albendazole, not in direct comparison to the intensive course.[6]

Albendazole (ALB) is a broad-spectrum antiparasitic used in combination with DEC or ivermectin (IVM) to enhance effectiveness.[8] Although there are reports of its effectiveness in combination,[4] its role has been controversial,[10] at least at MDA dosages.[11] It may be that the obvious symptomatic impact of ALB on intestinal parasites improves combination MDA compliance.[12]

Ivermectin also kills MF and may impair fertility of adult worms. It replaces DEC where onchocerciasis is prevalent. The dose of IVM employed in LF MDA is the same as for onchocerciasis (where no benefit of a higher dose has been shown).[3] Efficacy of IVM in LF, however improves at a higher dose (400 µg compared to the standard 150 µg[14]) although the real-world effectiveness (including cost-effectiveness) of the higher dose remains an unresolved question.

Use of DEC-fortified salt is acknowledged as an alternative to MDA. It has been employed on limited occasions but with success, notably in China.[13].

Inconsistent and prolonged use of MDA has potential for producing drug resistance, especially given uncertainty around the mechanism of action of DEC, the precise dose and drug combination that is likely to be most effective and for how long MDA should be used in specific settings.[14] Although DEC resistance may not be an issue,[6] resistance to albendazole has potential implications for treatment of intestinal nematodes with other benzimidazoles.

The place of vector control has (recently) been formally acknowledged in programs to address neglected tropical diseases but specific (global) strategies and programs are not well articulated. In view of the evidence that, in some areas (e.g. Africa, where anopheline species are predominant) vector control strategies are at least additive to MDA17 and in others, essential to breaking transmission (where the dominant mosquito species are efficient at low MF prevalence),[14,18] the absence of well-articulated vector control strategies is problematic.

On balance, LF MDA regimes were formalised early and are not ideal. They temporarily reduce microfilaraemia but require high levels of compliance over some years and have minimal practical impact on adult worms and morbidity.[14]

Parasite transmission

Overall, 50% of bancroftian filariasis is due to *Culex quinquefasciatus*.[16] *Anopheles* spp. are the major vectors in much of tropical Africa.[17] The biting, resting and breeding behaviour of *Aedes* spp. in parts of Asia and the Pacific present particular challenges for elimination.[18,19]

Filarial transmission is inefficient. The adult and larval worms, respectively, do not multiply in the mosquito vector or human host, and biting over months is required for sustainable infection.[20,21] In practice, this apparent inefficiency masks a complex relationship between vector, host, environment and parasite that is still not completely understood.[22] Figure 1 shows the parasite lifecycle.[23]

Vector-parasite density relationships are critical to LF intervention.[24] The existence of thresholds of MF density, below which transmission will not be sustained, is the basic assumption justifying GPELF.

In some mosquitoes, if the 1% MF prevalence target is achieved, ongoing transmission may not be sustainable,[18 25] because transmission in these vectors is inefficient at low MF levels. The threshold for interrupting transmission is therefore higher in these vectors. This has been called 'facilitation'.[28] *Anopheles* species exhibiting facilitation have a developed cibarial armature (a tooth-like chitin structure) that damages MF[26] and at low densities significantly reduces MF survival.[28]

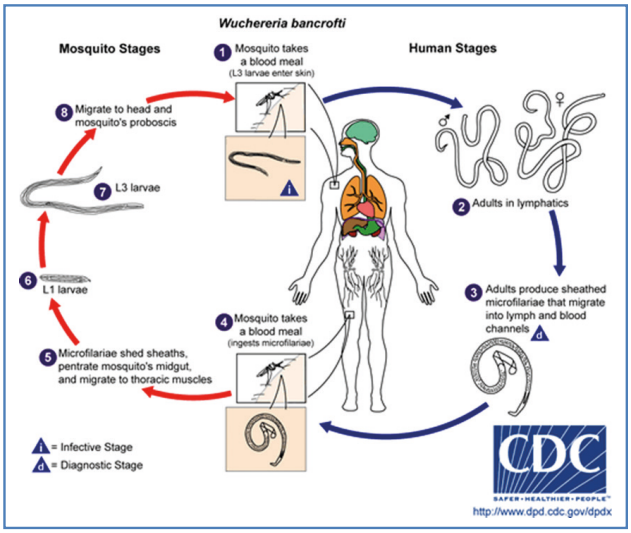

Table 1. Life cycle of *W. bancrofti*[23]

In other mosquitoes, although levels of infective stage larvae (L3) plateau at high levels of MF intake (referred to as 'limitation'),[28] transmission is efficient at low MF densities, resulting in a low elimination threshold. Limitation likely reflects the adverse effect of larger numbers of MF and/or larvae on mosquito survival.[28] This probably applies to all mosquito vectors but in some, control is facilitated where transmission is inefficient at low MF levels.

Limitation in *Aedes polynesiensis* (a vector of *W. bancrofti*) may explain MDA failure in Polynesia.[22] The variable distribution of LF where vectors exhibiting facilitation predominate (e.g. *An. gambiae*), the successful elimination of LF from the Solomon Islands (where *An. farauti* is the vector) due to malaria control strategies[21,22] and initial success of MDA in parts of Papua New Guinea (where *An. farauti, An. punctulatus, An. koliensis* and others, including *Culex* spp., are vectors)[27] are consistent with the facilitation hypothesis in anophelines.

Ultimately, the parasite thresholds in host, vector and environment are the key issues. The transmission breakpoint (TBP)[23] is the threshold at which a worm population is unsustainable and is a function of vector efficiency (effective biting rate, influenced by limitation and facilitation processes) and worm burden in the host (essentially, opportunity for worm survival and reproduction).[29]

In addition, as for malaria, the local potential for elimination is impacted by baseline endemicity[32] and the disease/vector importation rates (e.g. via population movements).[30] Local vector, host and environmental conditions interact to determine eradicability.

GPELF in action

Potential for MF reduction by MDA is accepted and models assuming adequate compliance and efficacy show a logical potential impact of MDA on morbidity. Nevertheless, evidence for effects on clinical disease is less certain.[6]

LF is a disease of poverty[32] and, although the vector-parasite-host dynamic provides a rationale for GPELF, vector breeding/survival[33] and environmental conditions[34] are critical. Improvements in economic conditions, especially sanitation, may be essential to elimination.[37,35]

China was declared free of LF in 2007, as was the Republic of Korea in 2008.[36] The National Programme of Agricultural Development in China commenced in 1956.[37] The program was overseen by one national institution with provincial and county level structures with many 'grass roots' organisations. The program was based on screening and targeted treatment. MDA was added in the late 1960s and DEC fortified salt in the 1970s, when MF prevalence had reached low levels.[40] The combination of MDA and selective individual treatment also underpinned elimination of brugian filariasis in the Republic of Korea.[38] Reports also highlight the importance of economic growth and improvements in living standards.[41] In Japan, the successful National Filariasis Control Program, commencing in 1962,[39,40] was based on effective community support and a nationally-coordinated strategy of screening and treatment.[43] Filariasis was eliminated from the Solomon Islands as a side benefit of an intensive vector control program aimed at eliminating malaria.[41]

Togo is the only sub-Saharan African country to reach the post-MDA phase (surveillance to confirm interruption of transmission).[42] The Togo National Program to Eliminate Lymphatic Filariasis (NPELF) commenced in 2000. The National Lymphoedema Management Program, established in 2005[43] is a central plank of the program. The MDA program built on an existing onchocerciasis program and community-based health structures. National and local leadership were critical as was adequate (and targeted) funding.[46] It remains to be seen if persistent transmission in other parts of West Africa, especially given spread of *Culex quinquefasciatus* from East to West Africa[44] and/or population migration from neighbouring countries,[45] results in resurgence in Togo.

The Tanzanian National Lymphatic Filariasis Elimination Programme (TNLFEP) also commenced in 2000. Significant progress was made initially and prevalence of MF was reduced; however, after three rounds of MDA this levelled off.[46] There is evidence that actual MDA consumption was less than that officially reported and that it fell over time.[47] Even those more positive about progress acknowledge low MDA coverage in much of the country and the challenge of managing 'vertical' programs in settings of scare human service resources.[48] Significant reduction in prevalence of MF in a coastal area in Kenya appears to have occurred despite inconsistent MDA but with effective (malaria-focussed) vector (*Anopheles* sp.) control.[49]

There are also inconsistencies between official reports and research surveys of MDA compliance in central Nigeria.[50] Nevertheless, reduction in MF (and antigenaemia) prevalence was shown (to less than 1% in some areas) after 7-10 years of MDA.[53] Failures correlated with higher baseline MF endemicity and antigenaemia.[53]

The Pacific Programme to Eliminate Lymphatic Filariasis (PacELF) commenced in 1999 in Samoa and now involves 22 countries,[21,22] although program reach is patchy.[51] There has been success with vector control in the Solomon Islands, MDA with vector control in parts of PNG, and (pre-dating PacELF) sanitation campaigns in Australia.[22] In Vanuatu MDA was ceased when MF prevalence dropped below 1%.[54] Variation in dominant vector transmission dynamics (*Anopheles* 'facilitation' in the Solomons, *Aedes* 'limitation' in 'resistant' areas) may be a major determinant of success/failure of MDA.[21]

South and South East Asia has the highest burden of disease, with 879 million people at risk in 2011.[52] The Maldives and Sri Lanka have reached the point of ceasing MDA and are in the post-MDA surveillance phase.[55] India has at least a third or more of global LF morbidity.[53] The Indian National Filaria Control Programme (NFCP) launched in 1955, with screening and selective treatment and vector control. Pilots of MDA (DEC) began in 1996 and were progressively scaled up as part of the National Vector-Borne Disease Control Programme (NVBDCP). Albendazole was added from around 2005.[56] The reported national MF rate has fallen to less than 1%.[54] The relevance of this is not certain. Many districts have higher rates and some have not been surveyed. Many districts reporting lower than 1% MF prevalence contain areas with higher rates.[56] In the 2011 census there were 640 districts in India.[55] Fewer than 200 (181) were targeted for MDA, comprising 72% of identified endemic districts.[55] Coverage of endemic districts peaked in 2006 (89%).[56] As elsewhere, MDA compliance is a serious challenge.[56]

Given the non-random distribution of LF, the level of compliance required is not clear. Lower coverage may be sufficient in areas of low baseline endemicity and vectors that are inefficient at low MF density. In other areas, MF prevalence below 1% may not guarantee disruption of transmission, e.g. expanding urban/peri-urban areas where *Cx. quinquefasciatus* (exhibiting transmission limitation) flourishes.[57,58] The predominance of another 'limitation' vector, *Aedes* species, in Samoa and French Polynesia, may explain the lack of success of a pure MDA strategy in eliminating LF even when MF prevalence fell below 1%.[6,59] Recently-reported MDA success in Egypt, where *Culex* species predominate, confirms the potential of MDA.[60] A sustainable break in transmission is, however yet to be proven nationwide, especially given that previous effective control was undone by vector resurgence, probably related to environmental changes and insecticide resistance.[61]

Discussion

This review was limited to articles published in English. Although the original search was limited to the past 5 years, relevant older articles were included. Reports that did not add substantive information have not been referenced but abstracts were reviewed. The focus was on review articles and reports and it is likely that some potentially relevant, especially unpublished, papers were missed. The papers included cover a spectrum of opinion, geographical area and experience and it is unlikely that the conclusions here would be altered by a limited number of missed publications.

There is no doubt that LF elimination programs have impacted MF prevalence and transmission, in some areas leading to local elimination of infection. Nevertheless, experience suggests that the GPELF may not have learned from previous (and ongoing) experience. An effective LF elimination strategy needs to be built on a detailed understanding of local community, environment and vector(s). Microfilariae prevalence can be significantly reduced given sufficient rounds of MDA. How many rounds are actually required is the question. Importantly, where certain vectors predominate and baseline endemicity[62] and disease/vector importation rates[33] are high, elimination is difficult and the risk of resurgence high. Local vector, host and environmental conditions interact to determine eradicability.[34] Long-term compliance with MDA is often problematic. Combining MDA with vector control seems likely to provide the best results[62,63] but community education and engagement are also required. Reports of the value of DEC-fortified salt suggest its role needs to be better articulated and supported.[64]

The reality may be that in certain localities (especially with vectors showing 'limitation' and close to other endemic populations), a realistic aim would be to reduce infection to a level (estimated at 3.5%) where chronic sequelae and disability are greatly reduced and become more manageable.[68] This might make individual therapy, such as doxycline for lymphoedema, feasible for implementation in targeted communities and individuals, and have spin-off benefits for other health services.

Elimination in many countries, and certainly on a global scale, seems unlikely given current knowledge, parasite/vector distribution, local governance and environmental conditions. Much has been accomplished but realistic disease specific strategies based on a synthesis of evidence with local objectives, not implementation of standardised interventions, should underpin national programs. This is especially critical given environmental changes due to agriculture, general environmental degradation or urban and peri-urban slum expansion in some areas that may be facilitating expansion of LF.[64,67]

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TARGETING THE SPOROZOITE: THE RTS,S MALARIA VACCINE

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ABSTRACT

Background: Malaria vaccine research and development has advanced rapidly over the past 20 years. This paper reviews the most advanced vaccine candidate, RTS,S, which is being evaluated in an ongoing phase 3 trial.

Methods: A systematic review of all randomised controlled trials identified from a search of the literature using MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and the reference lists of all the studies identified in the above search methods, was performed.

Results: Eight safety trials, six efficacy trials and eight follow-up extension studies were identified and evaluated for study methods, risk of bias, and safety and efficacy outcome measures. Studies were generally of high quality with low risk of bias. The RTS,S vaccine had no notable serious adverse effects and was highly immunogenic. Vaccine efficacy in phase two trials was 33-65% in infants and 30-53% in children for preventing the first episode of malaria. Early results of phase three studies have shown a reduction in clinical malaria of approximately 50% in children and 30% in infants, although efficacy seems to wane over time and with increasing malaria exposure.

Conclusion: The RTS,S vaccine is safe and immunogenic. The vaccine has been shown to be efficacious in clinical trials, although long-term follow-up is limited. Final analysis of phase three studies due in late 2014 will be important in guiding further research, development and implementation of an effective malaria vaccine.

Keywords: malaria vaccine, RTS,S, vaccine efficacy, randomised controlled trial

BACKGROUND

Malaria is a serious global health problem with profound social and economic consequences in developing countries. It is caused by protozoan parasites of the genus *Plasmodium*, transmitted by bites of infected female *Anopheles* mosquitoes. Five different plasmodium species are known to cause human infection (*P. falciparum, P. vivax, P. ovale, P. malariae* and the more recently-implicated P. *knowlesi*). The most widespread and most serious of these is *Plasmodium falciparum*. According to the World Health Organization (WHO), malaria is responsible for 219 million cases of disease and 660 00 deaths annually. An estimated 90% of deaths occur in sub-Saharan Africa, with children under five years most severely affected.[1] Malaria control, therefore, is a public health imperative.

Malaria is entirely preventable and treatable. WHO malaria mortality rates have decreased by more than 25% globally since 2000, and by 33% or more in the WHO African region.[1] Methods of vector control focusing on insecticide-treated bed nets and indoor residual spraying and improved diagnostic and treatment modalities have contributed to the overall reduction in malaria mortality. Despite these advances, the development of an effective vaccine is likely to be critical for complete malaria control.

The past decade has witnessed dramatic advances in malaria vaccine research and development. However, progress is complicated due to parasite size and antigenic diversity, complexity of the malaria life cycle, and difficulties in developing a sustained immune response.[2] To be effective, a malaria vaccine should either prevent infection altogether, or mitigate severe disease and death in those who have been infected. Ideally, it should be incorporated into the existing Expanded Program of Immunisation (EPI).

Vaccines can target four different stages of the malaria life cycle. Pre-erythrocytic vaccines target the first two stages, which include sporozoite inoculation into the human bloodstream by an infected mosquito and parasite development in liver cells. Blood stage vaccines target parasite invasion and growth in the red blood cell. The gametocyte stage, when parasites emerge from red blood cells and fuse to form a zygote within the mosquito, is the focus of transmission-blocking vaccines.[3] Most advanced studies have focused on pre-erythrocytic stages.

The most advanced and well-documented pre-erythrocytic vaccine candidate is RTS,S, a hybrid recombinant product derived from the circumsporozoite protein (CSP) that is found on the surface of the sporozoite, fused to hepatitis B virus surface antigen. It has been evaluated in combination with two different adjuvant systems (AS): AS01 and AS02. Clinical development is undertaken in a public-private partnership between GlaxoSmithKline (GSK) and the PATH Malaria Vaccine Initiative (MVI), which receives funding from the Bill and Melinda Gates Foundation.[2] The vaccine is being evaluated in an ongoing phase 3 trial involving 11 sites in 7 countries in children living in malaria-endemic areas in sub-Saharan Africa. This review will critically evaluate and summarise findings of all clinical trials involving the RTS,S pre-erythrocytic malaria vaccine, and assess its safety and efficacy against falciparum malaria.

METHODS

Search strategy

A systematic review of the electronic databases MEDLINE (May 1980-May 2013), EMBASE (May 1980-May 2013) and the Cochrane Central Register of Controlled Trials (CENTRAL) (May 1980-May 2013) was performed using the following search terms: Malaria OR plasmodium AND Vaccin* AND RTS,S. Results were limited to randomised controlled clinical trials of vaccines containing RTS,S, in humans of any age. The primary outcome measure was clinical malaria infection. Secondary measures included episodes of severe malaria, immunological response (presence of anti-CSP antibodies) and adverse events. Suitable studies were also identified by evaluating the reference lists in publications found using the above search strategy.

Study selection and data extraction

Each clinical trial was assessed for safety, immunogenicity and efficacy outcomes. For efficacy studies, clinical trials were included where they reported acquisition of malaria disease, defined as the development of fever (axillary temperature ≥37.5 °C) with documented *P. falciparum* parasitaemia. Severe disease was defined in each individual study. Information regarding study design, population, study period, inclusion and exclusion criteria, surveillance method, clinical outcomes and results were extracted.

Assessment of risk of bias in included studies

All studies were assessed for risk of bias by analysing method of generation of allocation sequence and allocation concealment; blinding (description of who was blinded including participants, investigators and outcome assessors); and completion of follow-up (proportion of randomised participants who completed all doses and completed follow-up).

RESULTS

Description of studies

Eight safety trials, 6 efficacy trials and 8 follow-up extension studies were identified and included in this review. Results of efficacy trials are summarised in Table 1.

Early phase 1 testing was conducted in 46 malaria-naïve adults, using experimental challenge with infected mosquitoes and hepatitis B vaccine as a control.[4] After promising results, a field trial was conducted in 306 Gambian males using rabies vaccine as a control. All participants were given a course of chemotherapy to clear parasitaemia before administration of the third vaccine containing 50 µg of RTS,S/AS02.[5] A booster dose was given to 158 participants the following year. Extended follow-up of safety and immunogenicity was reported after 5 years.[6]

Paediatric clinical development of the vaccine was conducted in The Gambia by conducting two sequential safety trials: a study in older children (6-11 years), followed by a study in younger children (aged 1-5 years). There were 90 children in the first trial and 135 in the second trial. Both studies used the rabies vaccine as control.[7]

A phase 1 safety trial was conducted in 60 children aged 1-4 years in Mozambique to ensure the results seen in The Gambia translated into similar safety profiles in Mozambique before a planned larger efficacy study in this population. Hepatitis B vaccine was used as control. The double-blind phase continued until 1 month after third vaccination, followed by a one-year open label phase.[8]

A 'proof of concept' trial was then conducted in Mozambique in 2 paediatric cohorts aged 1-4 years.[9] The first cohort comprised 1 605 children and mainly assessed protection against clinical malaria, whilst the second cohort of 417 children focused on new infections. The control vaccine for children <24 months was the pneumococcal vaccine (dose 1 and 3) plus *Haemophilus influenzae* b vaccine (dose 2). Children >24 months were given 3 doses of hepatitis B vaccine. All children in the second cohort received presumptive treatment with amodiaquine and sulfadoxine-pyrimethamine 4 weeks before the start of surveillance to clear any parasitaemia. Initial results were published at 6 and 18 months after the third dose.[9,10] Safety evaluation after 18 months[11] was later followed by an extended follow-up phase of 4 years for safety and efficacy[12] and immunogenicity.[13]

Recognising the need to prioritise intervention strategies in infants led to the phase 1/2b trials for safety and efficacy in children <12 months. A study of 214 children aged 6-12 weeks was conducted in Mozambique using hepatitis B vaccine as control. All participants received a combination of amodiaquine and sulfadoxine-pyrimethamine 2 weeks prior to dose 3 to clear parasites.[14] The results of the safety, immunogenicity profiles were reported for two different periods of follow-up: initial 6 months[14] and 14 months.[15] A further safety and immunogenicity trial was conducted in 340 Tanzanian infants aged 6-12 weeks using RTS,S/AS02D and hepatitis B vaccine as control.[16]

Preliminary data suggested better immunogenicity with the AS01 adjuvant than with AS02.[17] Phase 2 trials in children in Gabon and Ghana showed similar safety profiles and higher immunogenicity of AS01E compared with AS02D.[18,19] This led to the candidate RTS,S/AS01 being used in trials in further phase 2 and phase 3 testing in children.

A cohort of Kenyan and Tanzanian children was followed in one safety study[20] and one efficacy study.[21,22] 894 children aged 5-17 months were assessed for safety, immunogenicity and efficacy. The rabies vaccine was used as a control. Length of follow-up varied according to location – the Tanzanian cohort was followed up for 12 months and the Kenyan cohort 15 months post-3rd dose. Those in the Kenyan cohort underwent an extended follow-up after 4 years.[23]

To assess the feasibility of incorporating the RTS,S vaccine into EPI schedules, an open-label safety and immunogenicity study was performed in 511 infants aged 6-10 weeks in 3 centres in Ghana, Tanzania and Gabon.[24] The RTS,S/AS01 vaccine was introduced into the EPI on a schedule of 0,1 and 2 months and 0,1 and 7 months. Extended follow-up of safety and efficacy was reported after 19 months.[25] Because the 0,1 and 2 month schedule can be easily implemented into the EPI and is therefore associated with a higher coverage, it was selected for further assessment in phase 3 studies.

Figure 1. The RTS,S Phase 3 efficacy trial in seven African countries.

Reproduced from the Malaria Vaccine Initiative website at www.malariavaccine.org[26]

Phase 3 testing for the RTS,S/AS01 vaccine is now underway in a multicentre trial in seven countries in sub-Saharan Africa (Fig. 1).[27-29] A total of 15 460 children has been enrolled in 2 different age cohorts – 6 537 infants aged 6-12 weeks, and 8 923 children aged 5-17 months. In the 6-12 week old group the MenC vaccine was used as the control. Those in the RTS,S group received either a booster dose of RTS,S or a follow-up dose of MenC vaccine. Vaccines were co-administered with the OPV and DTPwHepB/Hib vaccines according to the EPI schedule. In the children aged 5-17 months, the rabies vaccine was used in the control group, and the RTS group received either a booster dose of RTS,S, or a follow-up dose of MenC vaccine. Preliminary data were reported 12 months after vaccination.[28] Final results are expected in late 2014.

Risk of bias

All RTS,S trials were generally of high quality. Randomisation was adequate in all studies. Allocation concealment was adequate in all studies except Kester (2001),[4] Agnandji (2010)[24] and the phase 3 trial, in which it was not used. All included studies were double-blinded, at least initially, except the open label EPI feasibility study.[24]

The paediatric trials in Mozambique[9,10,14] were double-blinded for the first 6 months, after which time the results were reported to study investigators. However, only the study statistician knew the randomisation code and no further immunisations were given after unblinding, so bias was unlikely to be a major issue.

In the trial by Kester,[4] only 24 of the 46 participants (52%) who were immunised were subsequently challenged (50% vaccine group; 58% placebo group). The Bojang study also had a relatively high loss to follow up: 14% of the vaccine group and 22% of the control group dropped out or were excluded between the first dose and the follow-up period in the first year. Only 52% of original participants took part in the second year of the trial (48% vaccine group; 56% control group). More than 94% of participants in each of the 2 paediatric trials from The Gambia completed the short follow-up.[7]

In children 5-17 months old in Mozambique, follow-up was better in the first cohort than the second. In the first cohort, 93% received 3 doses, and 86% completed follow-up to 6 months, compared with 92% and 72% respectively. More than 90% of participants entering the single-blind phase completed follow-up to 18 months. Both cohorts underwent an open-phase extended follow-up, of which more than 72% were analysed for outcome measures after 4 years.[12,13]

In the study in infants 6-12 weeks in Mozambique, 83% completed follow-up to 6 months,[14] and the same proportion completed one-year follow-up.[15] Ninety percent of participants in the study of Tanzanian infants completed follow-up until 9 months.[16]

The studies from Kenya and Tanzania were double-blinded for the first 8 months, after which time the investigators were unmasked. Ninety-seven percent received all 3 doses of vaccine, and 90% completed 8-month follow-up.[21] More than 93% completed 12 month follow-up[22] and a total of 320 children (72%) from the Kenyan cohort completed 4 years of follow-up.[23]

In the EPI feasibility study, 93% of participants completed follow-up to 8 months[24] and 88% completed follow-up to 19 months.[25] However, this was an open label trial, so inherently subject to observation bias.

In phase 3 clinical testing, 4 296 of the first 6 000 children (72%) enrolled in the 5-17 month age group were included in the per-protocol analysis 12 months after vaccination. In one study centre, vaccines were exposed to temperatures outside the recommended storage range, leading to the exclusion of 870 children from the per-protocol analysis.[28] Of the 6 537 infants enrolled in the 6-12 week age group, 6003 (92%) were included in the per-protocol analysis at one year.[29]

Effects of interventions

In one trial in non-immune people using experimental challenge, overall protective efficacy of RTS,S/SBAS2 was 41% (95% confidence interval CI 22%–56%; p=0.0006).[4] However, study size was small, no allocation concealment was used and a high number was lost to follow up.

In semi-immune adults in The Gambia, the RTS,S vaccine showed an acceptable safety profile, and an efficacy of 34% (95% CI 8-53%, p=0.014). Protection seemed to wane; estimated efficacy during the first 9 weeks of follow-up was 71% (95% CI 46-85%), but decreased to 0% (95% CI -52-34%) in the last 6 weeks. Vaccine efficacy in the subgroup that received a booster vaccine was 47% (95% CI 4-71%). Vaccination produced strong antibody responses to CSP, and strong T-cell responses.[5]

In Gambian children, RTS,S vaccine was safe at all doses across both age groups and all doses were highly immunogenic for anti-CSP and anti-HBsAg antibodies.[7] A similar safety profile was reported in the population of Mozambican infants aged 1-4 years. The RTS,S/AS02(A) vaccine induced high anti-CSP antibody levels with at least 96% of children remaining seropositive during the entire follow-up period.[28]

In the Mozambique trial, vaccine efficacy for the first clinical episode of malaria was 29.9% (95% CI 11-44%, p=0.004) and for severe malaria 57.7% (95% CI 16.2-80.6%, p=0.019) in the first 6 months of follow-up. After 18 months, vaccine efficacy for first clinical infection was 35.3% (95% CI 21.6-46.6, p=0.0001) and 48.6% (95% CI 12.3-71.1, p=0.02) for severe malaria.[10] In cohort 2, vaccine efficacy for extending time to first infection was 45% (95% CI 31.4-55.9, p<0.0001).[9] Results following the entire 4-year follow-up showed a sustained response, with vaccine efficacy against clinical malaria of 30.5% (95% CI 18.9-30.4%, p<0.001) and severe malaria 38.5% (95% CI 3.4-61.3%, p=0.045). Vaccine efficacy against all clinical malaria episodes was 25.6% (95% CI 11.9-37.1%, p<0.001).[12]

Safety trials conducted in the infant group in Mozambique reported no increase in serious adverse effects in the RTS,S group over controls.[14] The geometric mean titre of anti-CSP antibodies decreased from 199.9 to 7.3 EU/mL from 1 to 12 months post-3 doses of RTS,S vaccine, but remained 15-fold higher than in the control group. Estimated vaccine efficacy against clinical malaria was 33% (95% CI 24.3 to 56.9, p=0.076); however, the study was not powered to assess efficacy outcomes.[15]

In keeping with the studies from Mozambique, vaccination was also shown to be safe and immunogenic in Tanzanian infants. One month after vaccination, 98.6% of infants receiving RTS,S/AS02 had positive titres for anti-CSP antibodies (geometric mean titre 69.5; 95% CI 53.9-89.6). The efficacy against any infection 6 months after the third vaccine dose was 65.2% (95% CI 20.7-84.7%; p=0.01) and 43.2% (95% CI -47.1-78 %; p=0.24) for first clinical infection.[16]

In the study from Kenya and Tanzania, at the end of the initial 8-month double-blind phase, efficacy against first malarial episode was 53% (95% CI 28-69%, p=0.0005) and efficacy against all malarial episodes was 56% (95% CI 31-72%, p<0.001).[21] After 12 months, vaccine efficacy was 39% (95% CI 20-54, p=0.0005) for first or only clinical infection and at 15 months vaccine efficacy was 46% (95% CI 24-61%, p=0.0004).[22] Over the entire 4-year follow-up period, however, vaccine efficacy had waned to 32.1% (95% CI 11.6-47.8%, p=0.004) for first clinical infection and 24.3% (95% CI 1.9-41.6, p=0.04) for multiple episodes of infection. Vaccine efficacy decreased with increasing malaria exposure (p=0.001). In children with a malaria-exposure index that was average or lower than average, vaccine efficacy was 45.1% (95% CI 11.3-66.0%), but among children with a malaria-exposure index that was higher than average, it was 15.9% (95% CI –11.0-36.4%).[23]

RTS,S was safe and immunogenic in the EPI feasibility study.[24,25] Twelve months after dose 3, vaccine efficacy against first malaria episodes was similar for both schedules (0, 1, 2 month group, 61.6%; 95% CI 35.6-77.1, p<0.001; and 0, 1, 7 month group, 63.8%; 95% CI 40.4-78.0, p<0.001, according-to-protocol cohort).

Initial results of the phase 3 clinical trial in the first 14 months after first vaccine dose in the first 6 000 children in the 5-17 months group reported a vaccine efficacy of 55.8% (95% CI 51.3-59.8%) and 45.1% (95% CI 23.8-60.5%) against severe malaria. Serious adverse events were similar in the two study groups.[28] In the cohort of children aged 6-12 weeks, vaccine efficacy was 31.3% (95% CI 23.6-38.3%) and 36.6% (95% CI 4.6 to 57.7) for severe malaria in the per-protocol analysis. One month after administration of the third dose of RTS,S/AS01, 99.7% of children were positive for anti-CSP antibodies, with a geometric mean titre of 209 EU per millilitre (95% CI 197-222).[29]

DISCUSSION

Clinical testing of the RTS,S vaccine has shown no considerable increased risk of serious adverse effects compared with control vaccines. The vaccine induced a powerful immune response to anti-CSP antibodies, although responses seemed to wane with time. RTS,S reduced the number of episodes of malaria and prevented severe malaria in several phase 2 and 3 studies. In phase 2 trials, vaccine efficacy rates were 33-65% in infants and 30-53% in children for preventing the first episode of clinical malaria. In phase 3 testing, vaccination reduced clinical episodes of malaria by approximately one-half after 12 months follow-up, but results were more disappointing in the infant age group, at 31% vaccine efficacy.

Although the clinical trials of RTS,S were of high quality, there are some notable limitations. Field trials were limited to African infants, making it difficult to generalise results to other countries where malaria is endemic and where other malaria species (e.g. *Plasmodium vivax*) are prevalent. Further studies are required to assess vaccine efficacy in these areas. There is evidence that vaccine efficacy wanes over time and studies involved short follow-up periods. Long-term efficacy and need for booster is still unknown. Final results of ongoing phase 3 clinical trials will be important in guiding further development. Additionally, studies were not adequately powered to address important outcomes such as death and hospitalisation.

CONCLUSION

The RTS,S malaria vaccine has been shown to be safe, immunogenic and efficacious in clinical studies. However, vaccine efficacy appears to wane in follow-up extension studies and efficacy is reduced with increasing malaria exposure. Ongoing analysis and long-term follow-up of outcomes is needed.

Despite these discouraging results, clinical testing of the RTS,S vaccine has contributed to further understanding of the relationship between immune response, intensity of malaria exposure and vaccine efficacy. Data from these studies and results of ongoing phase 3 testing will be important in guiding further research, development and implementation of a malaria vaccine. Sustained global commitment, collaboration and funding and further vaccine research is needed to progress toward the goal of malaria control, elimination and ultimately eradication.

Table 1. Efficacy results from RTS,S vaccine clinical trials

Reference	Population	Follow-up	Intervention	Trial endpoints	Vaccine efficacy (95% CI): per protocol	Vaccine efficacy (95% CI): intention to treat
PHASE 1 AND 2 STUDIES						
Bojang 2001[5]	306 males 18-45y from The Gambia	15 weeks after 1st dose	RTS,S/AS02 (50µg/0.5mL) 3 doses on day 0, 28, 150; dose 4 the following year Rabies human diploid cell vaccine Sulfadoxine-pyrimethamine (3 tablets) given 2 weeks before dose 3	Time to first malaria infection (positive blood film) First or only episode of fever and any parasitaemia	34% (8-53) 31% (-7-56)	NA NA
	158 males 18-45y from The Gambia	9 weeks after 4th dose		First or only episode of fever and any parasitaemia	47% (4-71)	NA
Alonso 2004a[9]	2 022 children 1-4y in Mozambique: 1 605 (Manhica) (cohort 1)	8.5 months after 3rd dose	RTS,S/AS02A 3 doses (25 µg/250µL adjuvant) at 0, 1, 2 months Pneumococcal conjugate vaccine (<24 months; 1st and 3rd doses) plus Hib vaccine (2nd dose) or hepatitis B vaccine (>24 months; 3 doses)	First or only episode of fever and parasitaemia >2500/µL Multiple episodes of fever and parasitaemia >2500/µL	29.9% (11-44) 27.4% (6.2-43.8)	30.2% (14.4-43) NA
Alonso 2004b[9]	2 022 children 1-4y in Mozambique: 417 (Ilha Josina) (cohort 2)	6.5 months after 3rd dose		New infections (any parasitaemia)	45% (31.4-55.9)	NA
Alonso 2005[10]	1 605 children 1-4y in Mozambique (cohort 1)	18 months after 3rd dose		First or only episode of fever and parasitaemia >2500/µL Multiple episodes of fever and parasitaemia >2500/µL	35.3% (21.6-46.6) 29.8% (13.8-42.8)	32.8% (20.1-43.3) 32.4% (17.6-44.5)
Sacarlal 2009[12]	2 022 children 1-4y in Mozambique	45 months after 1st dose		First or only episode of fever and parasitaemia >2500/µL Multiple episodes of fever and parasitaemia >2500/µL	30.5% (18.9- 40.4) 25.6% (11.9-37.1)	NA NA
Aponte 2007[14]	214 infants 6-12 weeks in Mozambique	6 months after 3rd dose	RTS/S/AS02D 3 doses given at 10, 14 and 18 weeks of age Hepatitis B vaccine (*Engerix- B*) Amodiaquine and sulfadoxine-pyrimethamine given 2 weeks before dose 3	First or only episode of fever and parasitaemia >500/µL Any infection (any parasitaemia)	65.8% (25.3-84.4) 65.9% (42.6-79.8)	NA NA
Aide 2010[15]	214 infants 6-12 weeks in Mozambique	12 months after 3rd dose		First or only episode of fever and parasitaemia >500/µL Multiple episodes of fever and parasitaemia >500/µL	33% (-4.3-56.9) 25.9% (-15.7-52.6)	25.9% (-9.9-50) 24.3% (-12.9-49.2)
Abdulla 2008[16]	340 infants 6-10 weeks in Tanzania	6 months after 3rd dose	RTS,S/AS02D (25 µg of RTS,S) + DTPw/Hib vaccine - at 8, 12, and 16 weeks of age Hepatitis B vaccine (*Engerix*-B)	First or only episode of fever and parasitaemia >500/µL Any infection (any parasitaemia)	43.2% (-47.1-78) 65.2% (20.7–84.7)	41.8% (-32.9-74.6) NA

Table 1 (continued). Efficacy results from RTS,S vaccine clinical trials

Bejon 2008[21]	894 children 5-17 months in Kenya and Tanzania	4.5 - 10.5 months (mean, 7.9)	RTS,S/AS01E 3 doses at 0, 1, 2 months Human diploid rabies vaccine 3 doses at 0, 1, 2 months	First or only episode of fever and parasitaemia >2500/µL Multiple episodes of fever and parasitaemia >2500/µL	53% (28-69) 56% (31-72)	49% (26–65) 54% (31-69)
Olotu 2011a[22]	894 children 5-17 months in Kenya and Tanzania	12 months after 3rd dose		First or only episode of fever and parasitaemia >2500/µL Multiple episodes of fever and parasitaemia >2500/µL	39% (20-54) 42% (22-57)	39% (20-53) 44% (24-58)
Olotu 2011b[22]	447 children 5-17 months (Kenyan cohort)	18 months after 3rd dose		First or only episode of fever and parasitaemia >2500/µL Multiple episodes of fever and parasitaemia >2500/µL	46% (24-61) 51% (29-66)	37% (14-55) 44% (20-61)
Olotu 2013[23]	447 children 5-17 months (Kenyan cohort)	4 years after 3rd dose		First or only episode of fever and parasitaemia >2500/µL Multiple episodes of fever and parasitaemia >2500/µL	32.1% (11.6-47.8) 24.3% (1.9-41.6)	29.9% (10.3-45.3) 16.8% (-8.6-36.3)
PHASE 3 STUDY						
Agnandji 2011[28]	6 000 children aged 5-17 months from 11 centres in 7 countries in sub-Saharan Africa	12 months after 3rd dose	RTS,S/AS01 3 doses at 0, 1, 2 months plus booster RTS,S/AS01 RTS,S/AS01 3 doses at 0, 1, 2 months plus MenC vaccine Rabies vaccine 3 doses at 0, 1, 2 months plus MenC vaccine.	First or only episode of fever and parasitaemia >5000/µL Multiple episodes of fever and parasitaemia >5000/µL	55.8% (51.3-59.8)* 55.1% (50.5-59.2)*	50.4% (45.8-54.6)* 53.9% (49.6-57.8)*
Agnandji 2012[29]	6 537 infants aged 6-12 weeks from 11 centres in 7 countries in sub-Saharan Africa	12 months after 3rd dose	RTS,S/AS01 3 doses at 6, 10 and 14 weeks of age with OPV and DTPwHepB/Hib vaccines plus booster RTS,S/AS01 and OPV RTS,S/AS01 3 doses at 6, 10 and 14 weeks of age with OPV and DTPwHepB/Hib vaccines plus OPV and MenC vaccines MenC vaccine 3 doses with OPV and DTPwHepB/Hib vaccines plus booster MenC and OPV vaccines	First or only episode of fever and parasitaemia >5000/µL Multiple episodes of fever and parasitaemia >5000/µL	31.5% (24.7-37.6)* 33.0% (26.4-38.9)*	30.1% (23.6-36.1)* 32.9% (26.7-38.5)*

NA = not available
*97.5% CI

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PLAGUE – A FORGOTTEN THREAT TO THE MODERN WORLD

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Abstract

It is well known that plague has wreaked great havoc in past times, but many are unaware of how common it still is. With new technologies and the fresh global conflicts that are constantly arising, as well as the impending consequences of climate change, the threat of this disease finding its way back into modern societies – especially those of the western world – has never been greater.

Keywords: plague, epidemiology, vectors, climate change, bioterrorism

Backcground

Plague is an ancient disease that has haunted human populations for millennia, with some of its first known documentations appearing on an amulet from the Akkadian Erra Epic (c. 800-612 BCE), which was used as a means of warding off the disease, as well as a passage in the Tanakh (canon of the Hebrew bible) that is believed to have been written circa 630-540 BCE, and describes one of the first possible epidemics. It has been known to decimate populations, and there have been three major pandemics in more recent history; the Justinian Plague (541–750 CE) that resulted in over 100 million deaths, the Great Plague (including the 'Black Death'), (1334 –17th C), which is believed to have killed between 75-200 million people, and modern plague (late 19th C – present), which has so far resulted in approximately 10 million deaths. In the 3rd pandemic plague spread widely and rapidly with the aid of transport systems, particularly steamships. It was taken to new territories such as North America, southern Africa, India, Madagascar and Australia, and *Yersinia pestis* became established in some native rodent populations but not in others, as was the case in Australia. The disease is now seldom thought about until sporadic or imported cases occur in developed countries, even though larger outbreaks affect less-developed parts of the world. As such, this review is intended to highlight that plague is not just 'that disease' that killed so many in the past – it is still very much has this capability, and it should not be forgotten about so carelessly.

Methods

A search of peer-reviewed scholarly articles and works was conducted using the following key search terms: plague, *Yersinia pestis*, black death, recent cases, biowarfare, bioterrorism, and economic effects. Search engines used include Science Direct, the National Center for Biotechnology Information (NCBI) division of the US National Library of Medicine's PubMed, and also Google Scholar and Books facilities. The Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) websites were also consulted for accurate maps and statistics.

The pathogen

Plague is caused by the bacterium *Yersinia pestis*, an enterobacteriacene that can protect itself from the immune system of its host.[1-3] This bacillus lacks a protective capsule upon entering the host's bloodstream, leaving it vulnerable to phagocytosis by macrophages, the defending white blood cells. Once phagocytosed, the biochemistry within the macrophage causes the bacteria to develop an insulating capsule highly resistant to destruction, and the cell wall of *Y. pestis* also stimulates the white blood cell to produce a variety of tissue-damaging proteins. These proteins protect the bacteria from its host's immune system whilst creating a more sustainable microenvironment for bacterial growth.[1-73]

Forms of plague

There are three main clinical forms of plague infection; bubonic, pneumonic, and septicaemic plague.[1,2,4,5,7-12] Bubonic plague is the most common form of the disease. Following inoculation via fleabite, there is local multiplication and increased local capillary blood and lymph flow. This promotes the spread of infected phagocytes to the lymph nodes where they accumulate and form buboes.[1-3,5,7] Septicaemic plague occurs when the *Y. pestis* bacteria multiply in the bloodstream. It can arise as the primary form of infection following flea bites, or as a secondary infection if bubonic plague is left untreated. Once in the bloodstream, the bacteria go on to produce Gram-negative septicaemia with coagulopathy and damage to internal organs, bleeding and a high risk of death.[1,2,4,8,12] Pneumonic plague is the most easily transmissible form of the infection between humans. It can occur when bacteria circulating in the bloodstream secondarily infect the lungs (and can then spread via respiratory droplets), or via the inhalation of these airborne bacteria directly into the lungs. If the infection is acquired through the latter route, the inhaled bacteria can spread quite rapidly through the lymphatic system and potentially lead to primary pneumonic and/or septicaemic plague.[1,4,5,7-9,12]

Vectors, reservoirs and hosts

There are over one hundred different species and subspecies of flea that are able to carry and transmit plague; however, only four of these typically pass the infection on to humans.[13] The primary vector and most efficient carrier of *Y. pestis* is the oriental rat flea or *Xenopsylla cheopis*, with *Xenopsylla brasiliensis*, *Pulex irritans* and *Nosophyllus fasciatus* acting as minor vectors.[1,6,13,14] In Africa, however, *X. brasiliensis* is the predominant human plague vector.[1] The primary host of the oriental rat flea is the black rat, *Rattus rattus*, but the brown rat, *Rattus norvegicus*, is also a common carrier.[1,4,5,15] Other small mammals have also been implicated as reservoirs of significance in the transmission of the disease to humans. These include great gerbils, other species of rodents, marmots, rabbits, cats, dogs, and various species of squirrel.[4,5,9,10,15]

Transmission to humans

When a flea takes a blood meal from an infected host, it will ingest the circulating bacteria. These bacteria then multiply in the flea's gut, and due to the production of a coagulase by the microorganism, they form a gelatinous mass that will block the long, narrow opening to the gut. When the infected flea then goes on to feed on a new host, this gelatinous mass will prevent any blood from reaching the stomach. This causes the flea to starve and become frantic, leading it to regurgitate the ingested blood into the puncture wound of the host along with the bacteria. Faecal material laden with bacteria that is deposited near a bite site can also lead to a plague infection, as can any bacteria released when a flea is crushed over the puncture wound.[1,2,4,6,7,10,15,17-19] Humans can also contract plague directly from the small infected mammals that act as reservoirs. This is most frequently seen amongst those working with deceased animals - for example, hunters skinning a rabbit may become infected if the rabbit's blood comes into contact with any broken skin.[9] Humans as well as domestic cats that are infected with pneumonic plague can also spread the disease via infected droplets expelled when coughing, and those with bubonic plague can spread the disease directly through pus discharged from ruptured buboes.[4,5,9-11,18,19]

Recent plague outbreaks

Globally, between 1 000 and 3 000 cases of human plague are reported annually.[4,5,11,16] In the past few years there have been a number of well-publicised outbreaks of various forms of plague. The first of these occurred in January of 2009 in Algeria, where at least forty members of the terrorist group Al-Qaeda in the Land of the Islamic Maghreb (AQLIM) died from the infection.[20] Not long after, another outbreak occurred in Libya in June of 2009, where one person died among 16-18 reported cases.[21] In a remote town in northwest China, three people died, nine more were hospitalised and a whole town of approximately 10 000 people was quarantined in August of 2009.[22,23] The source of the outbreak was discovered to be the first victim's dog – the animal had eaten a marmot carrying infected fleas and had become their new host. Not long after the dog died from the infection, the fleas in turn transferred to the owner whilst he was burying the dog.[24] As well as these specific outbreaks, it is also reported that between one and seventeen people die annually from plague in the US.[4,5,9,16,25] Well over 90% of the confirmed deaths and overall cases of plague occur in Africa,[14] with statistics showing that the Democratic Republic of Congo has the most highly active foci of plague in the world, reporting more than 1 000 suspected human cases per year.[5] Plague is also common in the South American countries of Peru, Bolivia, Brazil and Ecuador.[4, 5]

Global distribution of *Yersinia pestis*

Figure 1 shows the recent geographic distribution of human plague, as well as indicating where major sylvatic foci or infected wild animals may be found.

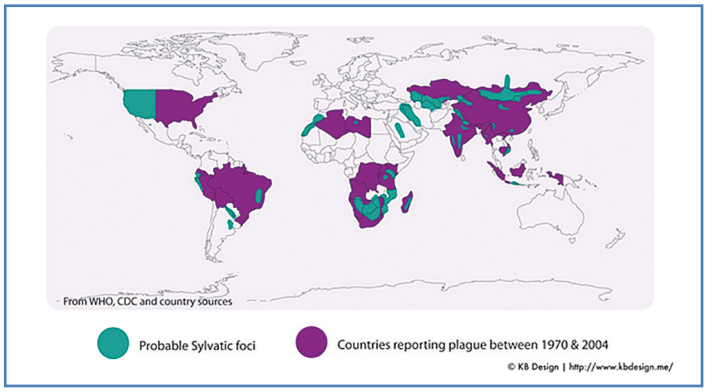

Figure 1. Global distribution of plague[16]

Global distribution of vectors and reservoirs

Plague is generally thought of as a 'disease of hot countries which has often invaded temperate zones',[15] and as such it is most commonly detected in late summer and early autumn. In spite of this, however, advances in technology have created artificially-maintained temperatures indoors, which may allow fleas to survive outside their natural habitat.[15] Figure 2 displays the current global distribution of three of the four fleas that commonly transmit plague to humans, as well as *Xenopsylla astia*, which is a major source of plague transmission between rats.[15]

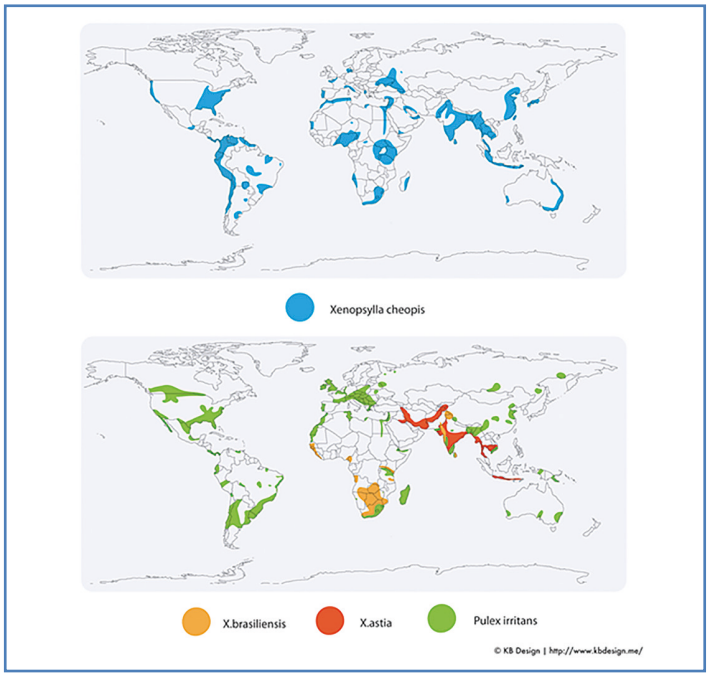

Figure 2. Geographic distribution of plague vectors.[26] Not shown is the range of *Nosopsyllus fasciatus*. This vector is prevalent on rats in Europe, temperate North America and Australia.[19]

Flea larvae hatch at an optimal temperature of 18-20°C in an environment with high relative humidity, and these conditions are often found in rodent burrows.[1] Warm, humid conditions favour the fleas, with dry heat being very hostile. Change in the general climate of a region, and particularly a change in the microclimates of rodent burrows, clay walls and the straw roofs of village

huts or slums, can instigate the fleas to migrate into human territory.[2,27] The vastness of the global distribution of both *Rattus rattus* and *Rattus norvegicus*, the primary hosts of these fleas, is astounding, ranging from the many tropical, subtropical and temperate climates found throughout Africa to the subantarctic climate on Macquarie Island.[28-30] The only areas of the world that are completely devoid of either of these species of rats are the Arctic, Antarctic, the province of Alberta in Canada, certain conservation zones in New Zealand, and some especially isolated islands.[31-34] The plague bacteria can also potentially be spread over long distances in many ways, including via mammal predators, birds of prey, and other birds that use rodent burrows for nesting. These animals generally move over larger areas than the rodents themselves, taking the infection with them. Humans are also able to travel over long distances, and although rare, cases of plague introduced in this way have been reported.[14]

Emerging patterns of plague

It has been observed that since the early 1990s there has been an increase in the incidence of plague, particularly evident in Africa. There are a few possible reasons for this increase; it may be linked to either a genuine increase in the activity of plague, an increase in the efficiency of the notification of cases to the World Health Organization, or a combination of both.[35] Another possible factor in this increase in human cases of plague may also be the global population explosion. As a result of the exponential increase in the human population, people move into previously uninhabited areas. This leads to more contact with wildlife, as well as unsuitable living conditions, such as overcrowding and poor sanitation, both of which may favour plague vectors and reservoirs.[27,36,37] In the last twenty years, outbreaks of human plague have been reported in at least three locations where cases of plague had been absent for the preceding 30-50 years. These outbreaks occurred in India during 1994 and 2002, Indonesia in 1997, and also in Algeria in 2003.[35] In each of the years these outbreaks occurred, the El Niño climate pattern had been present in the affected areas.[38]

Global warming and climate change

Figure 3 illustrates the predicted increase in global temperature using information from eight different environment-focused government bodies from around the world.

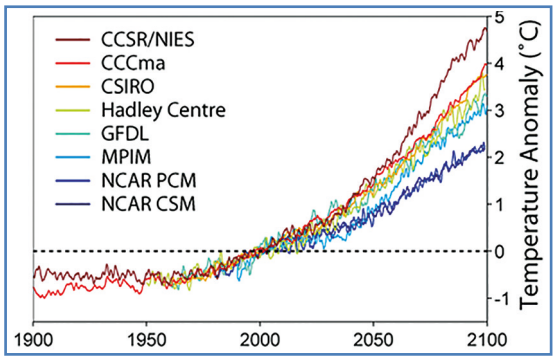

Figure 3. Projected increase in average global temperature according to various models (Robert A. Rohde/Global Warming Art).[39]

Overall, the projected outcome from global warming is that in the forthcoming 87 years, the average increase in temperature worldwide will be somewhere between 1.4-5.8°C, with a mean consensus of approximately 3.0°C. Figure 4 shows a somewhat homogeneous warming pattern on land, with the exception of South America. This is due to the predicted changes to the El Niño pattern, as well as the possible collapse of the Amazon rainforest. Also standing out is the Arctic region, where the temperature is predicted to increase by up to 9.2°C.[40]

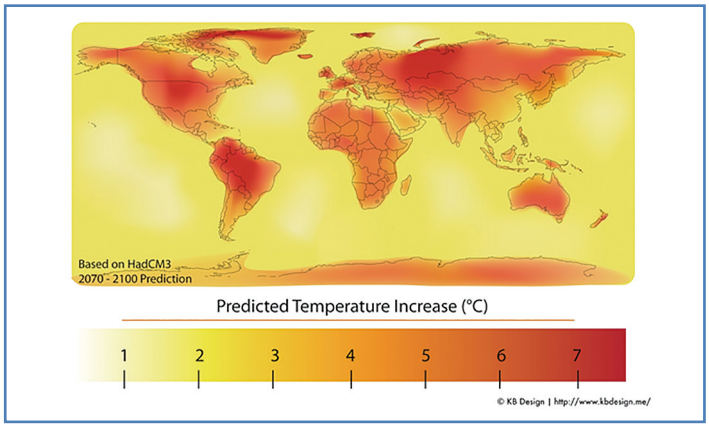

Figure 4. Predicted global warming at the end of the 21st century (Robert A. Rohde/Global Warming Art).[40]

These predicted climate changes may favour an increase in the prevalence of *Y. pestis* in the human population in some areas. Recent studies have estimated that for every 1°C increase in temperature that occurs during spring, plague host prevalence will increase by more than 50%.[14,27,37] Norwegian, American and Swedish scientists have identified a pattern between the incidence of plague infection in the US and the natural shift between warm and cool ocean currents. Before this study, the reason for the fluctuation in plague cases was unknown, with numbers ranging from almost no cases in the 1950s during a cool phase, to a very high (by US standards) incidence of 40 in 1983 during a warm phase. It is well-known that warm, wet conditions are favourable for both rats and fleas, as fewer rodents will die in milder winters and food is more readily available when there is more rain. However, the predicted climatic changes in the US indicate that the western portion of the country, where plague is currently most active, will become too dry to supply enough food for the current rodent population. It will also result in more heatwaves, which can be deadly to the flea vectors.[41] In contrast to the future predictions in the US, it is also believed that climate change may lead to plague infections becoming more prevalent in other parts of the world. Central Asia is a region thought to be a major contender in this, with changes forecast to move towards moister conditions.[41] Australia is also predicted to undergo some climatic changes in response to global warming, and the effects these may have on the incidence of plague infection are discussed below.

Potential risks for Australians

As previously discussed in regards to Figure 2, three of the four vectors that are able to transmit plague to humans can currently be found in Australia, and cases of plague infection occurred here in the past.[42] Changes to the Australian climate over the coming decades will reportedly involve an increase in cyclones and floods, as well as creating more low-lying, wet areas.[43] These will allow for more vegetation to grow, leading to a possible increase in both the number and distribution of rodents potentially acting as reservoirs. Additionally, there is always the possibility of imported cases of plague as a result of the ease of modern travel. However, this is a rare occurrence, with only one imported case being reported in the US since 1926.[27] Of particular concern is a possible outbreak in regions where there is warfare, and it is believed that 'plague responds to warfare in the tropics as typhus does in the temperate region'.[15] However, many of the persons believed to be at a high risk of contracting plague and importing it (for example military personnel) are immunised against the infection, more than likely attributing to the low frequency of importation.[44] Nevertheless, the efficacy of the current available vaccination is questionable, and it has been shown to produce adverse reactions.[5] Another complication related to the spread of plague infection is the discovery of new naturally multidrug-resistant strains of *Yersinia pestis*, such as that discovered in a 1995 case in Madagascar.[45] If these were to spread throughout the world, it could present the human population with a serious health hazard.[14,27,46-50]

The most worrisome risk of plague infection to Australians is the prospect of the bacterium being used as a biological weapon. This has occurred in the past, most notably in 1346 by the Tatars besieging the Genoese-controlled

port of Caffa (now known as Feodosiya, Ukraine).[7,27,51] More recently, the Japanese military Unit 731 reportedly experimented with various methods of deployment of *Yersinia pestis* during World War II, and reports during the Cold War suggested that both the US and the former Soviet Union were researching aerosolised forms of the bacteria, as well as having created multidrug-resistant strains.[6,27,51,52]

The World Health Organization has published a report stating that, as a worst-case scenario, the deliberate release of 50 kilograms of the *Yersinia pestis* bacterium in aerosolised form over a city of five million could result in pneumonic plague in up to 150,000 people with an estimated 36,000 possible fatalities. As well as this, bacteria would remain active in the area for one hour and up to a distance of ten kilometres, with the people in the targeted city more than likely to attempt an escape, further broadening the reach of the disease.[53]

The Centers for Disease Control and Prevention (CDC) have classified *Y. pestis* as a Category A select agent, indicating that it has been recognised as having a high potential for use as an agent of bioterrorism due to its pathogenicity and rapid spread.[14,27,52] The epidemiology of plague used as a biological weapon would be considerably different to that of naturally occurring plague. The most likely form of deployment would be as an aerosol, leading to an outbreak of pneumonic plague. This may be initially misdiagnosed in Australia as another form of respiratory illness due to the historic absence of plague infections, but the alerting features would be symptoms occurring one to six days following exposure to the bacteria, with most people dying not long after they present with illness. An indication that an outbreak of plague is the result of bioterrorism would be its occurrence in areas not known to have enzootic infections or risk factors for infection, and the absence of large numbers of deceased rodents.[5,51,54-56] Bioterrorism poses a risk of plague being reintroduced to Australia, and currently research is being done into the best way of producing another, more efficient vaccine.[5]

Conclusions

Plague outbreaks can have devastating consequences, and the effects can also be severe on the economies of those countries involved, as well as on agricultural and biological diversity. Those most at risk of being targeted with the disease in an act of biological warfare are western societies, and climate change and global warming will potentially produce ideal environments for the disease and its vectors to thrive in much of Australia – especially the tropical north.

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A REVIEW OF HOSPITALISED CASES OF DENGUE IN CAIRNS, QUEENSLAND, DURING A DENGUE SEROTYPE 3 VIRUS EPIDEMIC IN 2008-2009

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Abstract

A large outbreak of dengue serotype 3 virus infection occurred during the wet season of 2008/9 in the city of Cairns in Far North Queensland, Australia. Of the 915 reported cases of dengue 3 virus infection, there were 73 patients requiring 75 hospital admissions. When compared with a dengue 3 epidemic that occurred in 1997/8, the rate of hospital admission was lower, but there were more (six) recorded cases of dengue haemorrhagic fever. One of the patients had inappropriate antidiuretic hormone secretion in association with encephalopathy. Use of the previous diagnostic criteria for dengue haemorrhagic fever was associated with inability to classify many patients. There was one recorded death. Increasingly frequent outbreaks of dengue can be expected to be associated with more frequent occurrence of severe cases.

Introduction

The dengue virus is a single-stranded positive-sense RNA virus belonging to the Flavivirus genus, family Flaviviridae. There are four distinct serotypes of dengue virus distinguished by antigenic and genotypic characteristics.[1] In endemic areas all four serotypes may be circulating at any one point in time.[2] In non-endemic areas, such as Queensland, the serotype/s circulating depend on the geographical source of the index case.

Cairns is a large coastal city on the north tropical coast of Queensland, Australia. The city has a population of around 150 000 and is an international holiday destination. Cairns Base Hospital serves a population of over 253 000 people spread over 275 000 square kilometres. This area, known as Far North Queensland (FNQ), has been affected by many dengue fever epidemics over the last century.[3-6] *Aedes aegypti* is the vector for dengue virus in the region. Dengue outbreaks have become increasingly frequent. Dengue fever is not endemic to the region but the virus has been repeatedly introduced by an index case, usually a returned traveller or tourist, from an endemic area, usually Southeast Asia or Papua New Guinea (PNG).[7] Queensland has had numerous significant (more than 500 cases – see Table 1) outbreaks since 1885.[8]

The last major dengue epidemic in FNQ (total 1025 cases) commenced in September 2008 and ended in August 2009. In Cairns, all cases were caused by serotype 3 (915 cases).[8] Numerous patients were hospitalised and cases of dengue haemorrhagic fever (DHF) were seen. In this study we describe the characteristics of patients admitted to the Cairns Base Hospital during the 2008/9 epidemic and compare the experience with that which occurred in the same area in 1997/8. During the earlier epidemic, there were 496 notified cases and of these 98 (20%) were hospitalised.[9]

Table 1. Summary of major dengue epidemics in Far North Queensland

Year	Description
1879	First recorded outbreak in Queensland
1885	First fatalities recorded
1897	60 deaths, 30 of which children, first deaths attributable to DHF
1900-1955	Four epidemics
1981-1982	Den-1: Cairns, Townsville, Thursday Island; several deaths
1992-1993	Den-2: large outbreak Townsville, Charters Towers
1997-1998	Den-3: Cairns, Mossman, Port Douglas
2003-2004	Den-2: Cairns, Townsville, Torres Strait Islands; 892 cases, four DHF, two deaths
2008-2009	Den-3:Cairns including Port Douglas, Yarrabah, Injinoo, Mareeba; 915 cases, six DHF, one death

Methods

This was a retrospective chart audit of the outcomes and treatment of all patients admitted or discharged from the Cairns Base Hospital with a primary diagnosis of dengue fever between September 2008 and August 2009.

A list of confirmed dengue cases admitted to the Cairns Base Hospital during the study period was generated from data collected by the Tropical Population Health Unit Cairns, as well as data recorded by the clinical coding department at Cairns Base Hospital. Pathology tests performed by the public laboratory, Pathology Queensland, and the private laboratories serving the area were collected for patients included in the study.

The public laboratory utilised Panbio™ dengue IgM and IgG capture ELISA plus the Bio-Rad Platelia™ dengue NS1 antigen test kits for the entire period of the epidemic. Additionally, an in-house reverse transcription-polymerase chain reaction (RT-PCR) test was performed by the reference laboratory in Brisbane to serotype all positive specimens. Private pathology laboratories used the same antibody tests, with some specimens referred for RT-PCR if requested by the ordering doctor.

The individual medical records of each patient, Queensland Health's public hospital centralised electronic pathology information databank (AUSLAB) and an electronic radiology databank (PACS) were then interrogated for demographic information, symptoms, clinical findings, treatment, outcomes and the results of pathological and radiological investigations performed during the inpatient admission.

For this study, any mention in the inpatient or emergency department notes of myalgia, arthralgia or back pain was recorded as 'musculoskeletal' symptoms. Any note of fatigue, lethargy, tiredness or malaise was recorded as 'lethargy/malaise'. Any history of any form of headache, whether frontal, retro-orbital or global, was recorded as 'headache'.

All temperature charts, progress notes, transfer notes from the Queensland Ambulance Service (QAS) or the Royal Flying Doctor Service (RFDS) or other hospitals or general practitioners notes, were examined for signs and symptoms and especially for any record of the patients' temperatures. Where the presenting symptom was fever or feverishness, this was recorded as subjective evidence of fever, even if there was no recorded temperature.

Haemorrhagic manifestations included petechiae, ecchymoses or purpura, gastrointestinal or mucosal bleeding, or bleeding from injection or intravenous cannula sites, menorrhagia or a positive tourniquet test.

DHF was diagnosed on the basis of criteria commonly used until the recent publication of new classification of dengue illness severity.[10] Patients were classified as having DHF if they had fever, thrombocytopenia, evidence of bleeding and either haemoconcentration or haemodilution, as evidenced by a change of haematocrit of $\geq$20%.[11]

Two Papua New Guinean nationals were transferred for treatment to the CBH

intensive care unit from Port Moresby during the epidemic. One of these, a child, was the only case of dengue shock syndrome. These patients were not included in the review, as the infections were acquired in PNG.

Results

A total of 73 cases of dengue, requiring 75 admissions, was identified. Two patients were readmitted. The first was a 74-year-old man, readmitted five days after initial admission to the short stay ward for 'not coping at home alone' with his symptoms; the second, a 46-year-old man, was readmitted four days after initial discharge with worsening symptoms. One patient required intubation and was admitted to the intensive care unit.

The average length of stay was 3.9 days, with a range of less than one to 15 days. Forty-four percent of admissions were female. Three children ranging in age from five to seven years were admitted (Figure 1). Most patients were admitted in the months from January to April 2009 inclusive (Figure 2). The average time to admission from symptom onset was 4.1 days (range, less than one to 14 days).

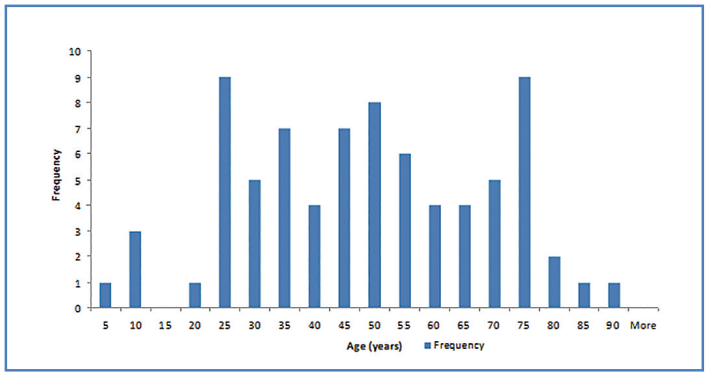

Figure 1. Age distribution of admitted cases of dengue fever to Cairns Base Hospital, 2008/9

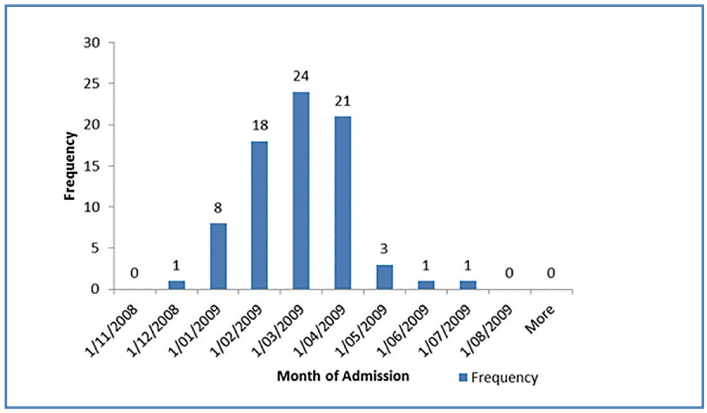

Figure 2. Number of admitted dengue fever patients per month, 2008/9

Six patients initially presented with a chest pain history of clinical concern. Three patients underwent echocardiogram, two had exercise stress testing and nine were admitted to a telemetry bed for observation. One patient had a CT chest scan without contrast and four patients had CT pulmonary angiography. Fifteen patients had cardiac enzymes assessed.

Gastrointestinal symptoms were frequent with nine patients undergoing abdominal ultrasonography and five having CT scans of the abdomen/pelvis. Five patients, including a six-year-old child, had a surgical review for abdominal symptoms or were admitted under a surgical team. An 82-year-old cognitively-impaired woman was reviewed by surgical teams on two occasions during the same admission to exclude a possible small bowel obstruction before the diagnosis of dengue was made. This was the only death thought to be, at least partly, attributable to dengue during the epidemic.

Six patients were admitted with confusion/delirium and 11 for an episode of loss of consciousness or presyncope; 53 complained of headache. Eight patients underwent a CT head scan and five had lumbar punctures.

With regard to classical symptoms of dengue, 43 patients had recorded temperatures of 38.0 °C or greater. Fifty-seven complained of fever at presentation and of those, seven recorded their temperatures and all had readings greater than 38.0 °C. Fifty-three patients complained of musculoskeletal symptoms and 24 had some form of rash. Clinical parameters and comparison with symptoms observed in the earlier epidemic are shown in Table 2.

Table 2. Clinical characteristics of admitted patients with dengue 3 in 2008/9 compared with 1997/9 (Horvath *et al* 9).

Symptoms at presentation	% frequency 2008-2009 *(n=73)*	% frequency 1997-1999 *(n=100)*	P value for difference
Any GI symptoms	87.7	84	-
vomiting	61.6	-	-
nausea	56.2	81	<0.01
diarrhoea	47.9	48	0.89
abdominal pain	32.9	-	-
anorexia	30.1	-	-
altered taste	2.7	38	<0.0001
Musculoskeletal symptoms	72.6	89	0.01
Headache	72.6	80	0.34
Complaint of fever	78.1	85	0.33
Inpatient temperature ≥38 °C	58.9	-	-
Lethargy/malaise	37.0	-	-
Rash	32.9	57	<0.01
Rigors	30.1	-	-
Cough	16.4	23	0.38
Haemorrhagic manifestation	16.4	19	0.82
Syncope/loss of consciousness	15.1	-	-
Photophobia	12.3	10	0.81
Pruritis	11.0	20	0.17
Chest pain	8.2	-	-
Confusion/delirium	8.2	-	-
Ocular pain	5.5	38	<0.0001

Laboratory investigations revealed that 45% of patients were neutropenic and approximately 55% were thrombocytopenic at some time during the admission. Nearly 80% had elevated aspartate transaminase (AST) levels, 65.8% had elevated alanine transaminase (ALT), and 74% had an AST: ALT ratio greater than 1.2. Three patients had AST levels over 1000 u/L; one of these patients had DHF, and had the highest AST recorded for the epidemic at 1500 u/L. Just over 80% of those whose C-reactive protein (CRP) was tested (n=52) had elevated levels. Laboratory findings and the comparative findings in the earlier epidemic are presented in Table 3; investigations performed are in Table 4.

Table 3. Laboratory findings during admission, 2008/9 vs 1997/9

Laboratory variable	% frequency 2008-2009 (n=73)	% frequency 1997-1999 (n)	P value for difference
WCC <4.0 x 10^9/L (RR* 4-11 x 10^9/L)	57.5	80 (100)	<0.01
Neutropenia <2.0 x 10^9/L (RR 2-8 x 10^9/L)	45.2	72 (100)	<0.01
Lymphopenia <1 (RR 1-4 x 10^9/L)	59	82 (100)	<0.01
Thrombocytopenia <100 x 10^9/L‡ (RR 140-400 x 10^9/L)	54.8	81 (100)**	N/A
AST >40 U/L	79.5	90 (93)	<0.01
ALT >45 U/L	65.8	77 (93)	0.02
AST:ALT >1:1.2	74.0	-	-
CRP >5 mg/L	57.5	-	-
Haematocrit change ≥20%	57.5	-	-

*RR: reference range

**Horvath *et al* defined thrombocytopenia as <140 x 10^9/L

‡WHO defines thrombocytopenia as <100 x 10^9/L

Table 4. Further investigations, dengue fever cases, 2008/9

Investigation	% received (n=73)
Plain chest X-ray	65.8
CT scans total	27.3
- head	11
- abdomen/pelvis	6.8
- CT pulmonary angiography	5.5
- chest	1.4
Abdominal ultrasound	12.3
Plain abdominal X-ray	8.2
Lumbar puncture	6.8
Echocardiogram	3.9
Telemetry	12.3
Exercise stress test	2.6

The majority (93.2%) of patients received intravenous fluids at some point during the admission. Just over 52% received antibiotics; six patients were placed in neutropenic isolation. No patients received blood transfusions and one patient received donor platelets. Treatments administered are shown in Table 5.

Table 5. Dengue fever inpatient treatment, 2008/9

Treatment	% received (n=73)	Total volumes received
IV crystalloid or colloid	93.2	Mean= 6 585 ml (Range 0-22 000 ml)
Platelets	1.4	3 units
Packed Red Cells	0	
Antibiotics	52.1	
Neutropenic isolation	8.2	
ICU admission	3.9	

Six patients met the WHO criteria for DHF and 42 patients met the haemoconcentration criteria, but did not display clinical signs of bleeding. None of these cases had a Hess test performed at any time during the admission. Four patients did not meet haemoconcentration criteria but fulfilled criteria for clinical bleeding. Ten patients met three of the four criteria, twenty-nine patients met two criteria, and 28 patients met one or none of the criteria for DHF.

The first case of DHF was a 48-year-old woman who presented with a one-day history of confusion, ataxia, headache, agitation and dysarthria. She had been unwell with fevers, vomiting, lethargy, arthralgia and general malaise for 4 days prior to the presentation. She was intubated and ventilated for 24 hours shortly after presentation due to deterioration in level of consciousness. A CT head and abdominal ultrasound were normal. She required inotropic support and received ceftriaxone and acyclovir until the serology results confirmed dengue. During her admission her sodium reached a nadir of 113 mmol/L leading to a diagnosis of syndrome of inappropriate antidiuretic hormone (SIADH). The platelet nadir was 74 x 10^9/L. Petechiae at the site of the blood pressure cuff and bleeding from an IV cannula site were noted during her admission. There were no recorded fevers during the admission. She recovered and was discharged from hospital 6 days after admission. The serological pattern was that of a secondary infection.

Case two was a 41-year-old man who presented at day two of his illness with a fever of 39 °C, chills, headache, myalgia, vomiting, diarrhea, rash, hematuria, epistaxis and petechiae. His platelets reached a nadir of 7 x 10^9/L at day six of his illness. He was treated with a total of 17 litres of intravenous fluids and simple analgesia over his admission of six days. He was discharged well.

Case three was a 28-year-old female Nepalese refugee who did not speak English, and who complained of a five-day history of fevers, nausea, vomiting, retroorbital headache, burning eyes, itch, abdominal pain and haemoptysis. She had presented to her family doctor on two occasions on days one and five and to the emergency department on days three and five of her illness before she was admitted. She was noted, whilst an inpatient, to have dried blood around her gums, haematuria, several coffeeground vomits, fever of 38 °C and platelet count nadir of 61 x 10^9/L. A gastroenterology review was requested by her admitting team because of very high transaminase levels, with AST peaking at 1500 u/L - the highest recorded during the epidemic. She was discharged after receiving a total of 22 litres of intravenous fluids, antiemetics, paracetamol and vitamin K over the ten days of her admission.

Case four was a 25-year-old woman who presented with a five-day history of fevers, retro-orbital headache, myalgia, arthralgia, nausea, vomiting, diarrhoea, mild abdominal pain and epistaxis. Her platelet count nadir was recorded as 18 x 10^9/L. There was no recorded fever during her overnight admission. She was treated with 5 litres of intravenous fluids and simple analgesia and discharged symptomatically well.

Case five was a 53-year-old man who presented to his LMO at day two of his illness then to the emergency department at day four with fevers, rigors, sweating, insomnia, nausea, vomiting, myalgia, lethargy, severe frontal headache and dizziness. He was febrile to 39.4 °C, which defervesced on day five of his illness. On the same day his haematocrit peaked at 0.5. There was no initial evidence of bleeding but at day 7 his platelet count dropped to 10 x 10^9/L and he developed haematemesis, melaena and haemoptysis. He was treated with a total of eight litres of intravenous fluids, simple analgesia and antiemetics and was discharged well after a five-day admission.

The sixth case was a 44-year-old man who presented to his LMO on day three then to the emergency department on day five of his illness with rigors, high fevers, occipital headache, anorexia, arthralgia, true night sweats, vomiting, a 'tight and bloated' abdomen, a petechial rash and bruising and a platelet count of 19 x 10^9/L. Pleural effusions were noted on CXR which, in the absence of a rise in haematocrit, fulfilled DHF criteria. He was also the only patient to have received a platelet transfusion. He received 5 litres of intravenous fluids and was discharged well after 2 days. There were no fevers recorded during his admission.

All six cases had positive dengue IgG serology at presentation, in addition to confirmation of a current episode of dengue fever.

Discussion

The most significant difference between the outbreaks of 1997/8 and 2008/9 was perhaps the most concerning. In 1997/9 there were only two cases of DHF out of nearly 500 cases reported, despite the rate of admission with other forms of dengue fever being considerably higher. During 2008/9 we were able to retrospectively diagnose six cases of DHF and the total number of confirmed cases of dengue was over 1000.

Laboratory results for the total white cell count, lymphocyte, neutrophil and platelet counts, ALT and AST differed significantly with the earlier outbreak having a greater frequency of laboratory abnormalities. The most frequently abnormal result for both epidemics was an elevation in AST (90% vs 79.5% respectively) with lymphopenia being second most common for both.

The difference in numbers of reported cases of dengue and DHF and laboratory abnormalities can be explained in a number of ways. The addition of the Bio-Rad Platelia™ dengue NS1 assay to those tests available in 1997/8 assisted in making the diagnosis of dengue earlier in the illness in 2008/9. This test has a sensitivity of 73.6% overall but it is higher in primary infections and earlier in the illness.[12] Specificity varies from 98-100%.[13,14] In the 11 years between the Den-3 outbreaks there were two outbreaks of Den-2 in 2003/4, totalling 892 diagnosed cases. Thus the 2008/9 outbreak may have included a higher proportion of second dengue infections with a heightened risk of DHF.

Both epidemics were caused by DEN-3. Of the four serotypes, DEN-2 and DEN-3 are observed to cause more severe outbreaks.[15] The sequence of dengue infection and which serotype is first encountered also has a direct effect on the outcome of subsequent infections. For example, Cuban adults with DEN-1 infection followed by DEN-3 had worse outcomes than those infected by DEN-2 followed by DEN-3.[16] The dengue outbreaks in Queensland have been closely monitored, however, and whilst there was an outbreak of DEN-1 in 2008/9, it occurred in an area approximately 300 km south of the area of interest.

The age of the six DHF cases ranged from 25 to 48 years with a mean of 39.8 years. There were no cases of DHF amongst children in 2009. All six DHF cases were IgG positive early in the course of illness and this is consistent with the observation that DHF is more common in secondary infections.

Regarding symptoms, there was little difference between the two outbreaks. The only difference in symptoms to reach statistical significance were nausea, rash, altered taste and ocular pain. The earlier outbreak recorded much higher numbers for the latter two symptoms (38% versus 2.7%, $p<0.0001$, and 38% versus 5.5%, $p<0.0001$, respectively). Both reviews were retrospective chart audits, so unless documentation standards had deteriorated significantly over the 11 years, this is likely to be a true difference. The authors of the earlier review remarked on the unusual severity of illness caused by this particular strain. Musculoskeletal symptoms (and headache for 2008/9), fever and GI symptoms were the three most common complaints for both outbreaks. This is not unexpected as fever and myalgia/arthralgia were also the most common symptoms recorded in caucasian adults resident in Thailand during a dengue epidemic in 1962-1964.[17]

Despite the publicity surrounding the dengue epidemic, there was a substantial number of patients treated with antibiotics and a large number of radiological investigations performed. The costs of delayed diagnosis and inappropriate antibiotics and investigations have not been calculated. Symptoms such as chest pain were most expensive in terms of time and resources. There were 19 CT chest scans, CTPAs, exercise stress tests, echocardiography or telemetry monitoring procedures performed.

Acute abdomen,[18] acalculous cholecystitis,[19] fulminant hepatitis,[20] encephalopathy/encephalitis,[21] and dengue meningitis[22] have all been reported as less common presentations of dengue infection. The management of the less common presentations is supportive, as surgical interventions have been shown to be associated with worse outcomes due to the increased risks of bleeding.[18,19] Understandably the major concern for many physicians would be in missing an alternative life-threatening diagnosis such as an acute surgical abdomen, bacterial meningitis, cardiac ischemia or acute hepatitis. For these reasons the World Health Organization has published new guidelines for the diagnosis and treatment of dengue infection to assist in classification and prediction of severe dengue cases.[10] This more practical schema assists medical staff to decide on the level of observation and treatment for each case at presentation. However, in the absence of serological confirmation, the overall pattern of fever, rash, myalgia, headache and GI symptoms plus leukopenia, thrombocytopenia and elevations of transaminases have been found to be the most useful in differentiating dengue from other febrile illnesses.[23]

Returning travellers and visitors from endemic areas, especially in SE Asia and PNG, constitute the greatest risk for introducing dengue into FNQ. The increasing frequency of dengue outbreaks will hopefully lead to better educated and more aware medical staff in the community and in the major hospitals in FNQ. Dengue accounts for 16% of fever in returning travellers and is second only to malaria as a reason for hospitalisation in tourists returning from tropical areas.[24]

With an increase in population in the region and increasing numbers of travellers from SE Asia plus the mobility of Torres Strait Islander and Papuan New Guinean populations, dengue outbreaks are likely to become more frequent, with the occasional occurrence of larger epidemics. The ability to rapidly diagnose new cases of DF and appropriately triage those with the potential to develop into severe dengue, will require education, improved use of better diagnostic tests and clearer clinical criteria. As dengue can be clinically indistinguishable from other febrile illnesses, a high level of suspicion and awareness on the part of physicians is required to minimise unnecessary diagnostic modalities and use of unnecessary treatment like antibiotics and surgery. The timely use of intravenous fluids and appropriate admission criteria has the potential to save lives by early detection and avoidance of severe dengue syndromes.

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