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Tuberculosis (TB), caused by the bacterium *Mycobacterium tuberculosis*, remains the second leading cause of mortality worldwide behind human immunodeficiency virus (HIV) infection, with 1.5 million deaths reported in 2013. In that year, there were also about 9 million cases of TB reported and of these there were 1.1 million HIV-positive new TB cases. Almost all of the deaths from TB occur in low to middle income countries; however, with global migration many high-income countries also have to deal with cases of imported TB. For example, in 2011, the TB notification rate in Australia was 1.0 per 100,000 for the general population, compared to a TB rate of 20.2 per 100,000 for the overseas-born population, with the highest rates in people from Nepal (284), Ethiopia (260) and Papua New Guinea (PNG) (238), reflecting similarly high rates of TB in these countries. The TB rate in the Australian-born indigenous population was 4.9 per 100,000.

For Australia, TB also represents a significant biosecurity challenge for health systems servicing the Torres Strait, as well as in migrants. TB is being diagnosed in PNG nationals accessing health care in the Torres Strait Protected Zone near the Australia-PNG border, where there were 47 cases of TB notified in 2011, a 42% increase from the year before, and which represents 20% of the TB case load for Queensland in that year.

Globally, TB remains one of the top 5 killers of women aged 15-44 years. Of the approximately 9 million new cases of TB reported in 2013, about 550,000 of these were children. In this issue, Comery examines the burden of paediatric tuberculosis, in the context of what he describes as a scarcity of accurate epidemiological data, related to ineffective screening and diagnostic capacity in high-burden countries.

Pulmonary TB is a common presentation; however, about one-third of the world’s population has latent TB, where people have been infected by TB bacteria but have yet to exhibit symptoms of disease. Common symptoms of active pulmonary TB are cough with occasionally blood-stained sputum, chest pains, weakness, weight loss, fever and night sweats. TB is usually transmitted from person to person via droplets from patients with active pulmonary disease. However, there are a myriad of extra-pulmonary presentations of TB, and miliary or disseminated TB, usually seen in children, is being more frequently seen in adults due to the prevalence of immunosuppression, which may be related to HIV infection, immunosuppressive therapies, and chronic haemodialysis programmes. In this issue, Aye et al describe an unusual case of disseminated TB in an immunocompetent 16-year-old patient. TB is a great mimicker and its various presentations can be confused with other conditions. It can be particularly difficult to diagnose in children. Nonetheless, early diagnosis is essential so that treatment can be commenced, especially in cases of miliary TB, which can be rapidly fatal.

The mainstay of TB diagnosis remains laboratory examination of sputum smears for the typical acid-fast bacilli; however, detection can be more difficult in less infectious forms of TB. Australia has guidelines for mycobacteriology laboratories undertaking diagnostic and drug susceptibility testing, which can be found elsewhere. The diagnosis of latent TB infection (LTBI) remains a challenge and, although tuberculosis skin testing remains the preferred method, guidelines exist in Australia for the appropriate use of interferon-α (IFN-α) release assays or IGRAs, which are more specific in patients with previous Bacille Calmette-Guérin (BCG) vaccination or exposure to nontuberculous *Mycobacterium* species.

Effective treatment regimens, normally a supervised administration of a six-month course of four anti-TB drugs, are available and appear to reduce the number of cases of TB; however, drug resistance is becoming an increasing challenge. In 2013, about 450,000 of the approximately 9 million cases reported were classified as multi-drug resistant TB (MDR-TB). There are also cases reported of extremely drug-resistant TB (XDR-TB) reported, as well as TB cases that appear to be totally resistant to currently available drugs. In this issue, Eaton and Ware outline the development and current knowledge relating to the molecular basis of TB resistance, particularly of MDR-TB, and discuss its implications for global health. Current Australian treatment guidelines are given in Therapeutic Guidelines-Antibiotic.

Other articles in this issue include an interesting case of Buruli (Bairnsdale) ulcer presenting in a farmer in rural New South Wales, Australia, reported by Fernando and Rana. Buruli ulcer is caused by a relative of *M. tuberculosis*, *Mycobacterium ulcerans*. Buruli ulcer is the third-most common mycobacterial infection worldwide, after TB and leprosy, in immunocompetent patients. The case illustrates the importance of thinking about Buruli ulcer in a patient with a non-healing ulcer with a relevant occupational, lifestyle and travel history.

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**References**

THE GLOBAL IMPACT OF THE EMERGENCE OF MULTIDRUG-RESISTANT TUBERCULOSIS

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Abstract

Approximately 12 million people worldwide suffer from tuberculosis, caused by the acid-fast bacillus Mycobacterium tuberculosis (MTB). The association of MTB infection with a number of conditions including human immunodeficiency virus, diabetes mellitus and malnutrition, along with the microbe’s increasing drug resistance, have been shown to aid the spread of infection. It is a growing public health concern worldwide, as resistant strains are difficult to treat, leading to increased mortality rates. This review outlines the development and current knowledge relating to the molecular basis of MTB resistance, particularly MDR-TB and discusses its implications for global health.

Keywords: tuberculosis, MDR-TB, XDR-TB, drug resistance

Introduction

Tuberculosis (TB) affects approximately 12 million people worldwide and is caused by the acid-fast bacillus Mycobacterium tuberculosis (MTB). Pulmonary infection is the most common presentation; however infection may occur in various sites, including the central nervous system and a disseminated (miliary) form. It also includes an asymptomatic, latent infection. It is only transmitted via droplets from active cases of pulmonary TB. Latent infection may subsequently activate to clinically apparent disease upon immunosuppression. Such cases cannot be determined through standard isolation and culture of the microbe, making diagnosis extremely difficult.

The emergence of drug resistance in MTB is a widespread issue. Multidrug-resistant tuberculosis (MDR-TB) and, increasingly, extensively drug-resistant tuberculosis (XDR-TB)* are growing public health concerns worldwide perpetuated by ease of transmission of MTB and inappropriate or incomplete treatment. This review outlines the development and current knowledge relating to the molecular basis of MTB resistance, particularly MDR-TB and discusses its implications for global health.

Demographics of tuberculosis

Worldwide distribution

The World Health Organization (WHO) estimated that 8.6 million new cases of TB occurred worldwide in 2012; it is likely, however, that only two-thirds of these were reported to national TB control programmes. A promising trend in global incidence has been seen in recent years with rates falling by approximately 2% per year. The highest burden of TB occurs in Asia (58%) and Africa (27%; Figure 1A).1

The WHO estimates that 3.6% of new cases and 20% of previously-treated cases worldwide in 2012 were MDR-TB. Europe and central Asia have the highest incidence of drug-resistant strains (Figure 1B). Approximately 9.6% of MDR-TB cases also met the criteria for XDR-TB.1 Alongside the MDR-TB burden, other chronic conditions are associated with an increased prevalence of TB. Table 1 outlines the prevalence of these at risk groups and the immunological basis by which they are thought to increase the prevalence of TB.

*MDR-TB is resistant to at least rifampicin and isoniazid, the two main tuberculosis drugs, while XDR-TB is additionally resistant to drugs used in the treatment of MDR-TB.
A close relationship exists between TB and acquired immunodeficiency syndrome (AIDS) (Table 1). Shenoi et al. estimate that nine percent of TB cases in adults are attributable to HIV/AIDS, while the WHO estimates that approximately 34% of global TB deaths are among HIV-positive individuals.\textsuperscript{1,3} It is also estimated that up to 10% of HIV-positive individuals have undiagnosed TB at the time of HIV diagnosis. The majority of countries listed by the WHO as having a high TB and MDR-TB burden also have a corresponding HIV burden. The likelihood of having concurrent MDR-TB is approximately 24% higher among HIV-positive than HIV-negative individuals and HIV co-infection with drug-resistant strains is associated with higher case mortality rates.\textsuperscript{1,3,5}

The risk of a diabetic individual contracting TB can be as much as eight times higher compared to a non-diabetic; however, a weaker association between diabetes mellitus (DM) and TB is seen in studies that adjust for socioeconomic status (Table 1). Cross-sectional studies have indicated that amongst patients with concurrent Type 2 DM and TB (DMTB), the percentage with MDR-TB is higher than that of drug-susceptible TB. Such DMTB patients typically require longer treatment regimens (\textless 1 year for drug susceptible TB), and have a higher chance of treatment failure or developing further drug resistance. The exact nature of the interactions between DM and TB, particularly MDR-TB, is yet to be determined.\textsuperscript{6-8}

Malnutrition is closely linked to TB infection; however, little is known about the exact molecular mechanisms involved (Table 1).\textsuperscript{9} Whilst studies have found between 20% and 100% of TB cases are also malnourished, it is not clear whether the malnutrition is a predisposing factor to, a result of MTB infection, or both.\textsuperscript{10,11} In a recent study it was found that more severe side effects of MDR-TB treatments were experienced by individuals who were underweight. In this group there was a two-fold increase in the risk of death during the treatment phase.\textsuperscript{12} It has been suggested that dietary supplements may reduce the risk of TB and MDR-TB and improve outcomes; however, there is currently a lack of evidence to support this suggestion.\textsuperscript{9,10}

Drug resistance

Emergence and development of drug resistance

The WHO defines MDR-TB as resistant to at least rifampicin (RIF) and isoniazid (INH), while XDR-TB combines MDR-TB with further resistance to at least three of the six classes of second-line drugs: aminoglycosides, capreomycin, fluoroquinolones, thioamides, cycloserine and para-aminosalicylic acid.\textsuperscript{1,13,14} The discovery of streptomycin in 1944 and isoniazid in 1952 provided means to treat TB, yet by 1960 reports of resistance to these drugs were entering the literature.\textsuperscript{15,16} Discovery of rifampicin in 1966 provided a new treatment option until the 1980s, when a resurgence of TB occurred. It was not until the early 1990s that MDR-TB was confirmed as the cause of this outbreak.\textsuperscript{13,15} Preliminary reports of XDR-TB began around 2004 and by 2007 it had been identified across six continents.\textsuperscript{13} New strains of MTB that are resistant to all drugs currently used for TB treatment are now being reported.\textsuperscript{15} These strains pose a major risk to public health and TB control initiatives as they are untreatable and have high mortality rates.\textsuperscript{16}

Low-frequency spontaneous chromosomal mutations have been identified as the cause of drug resistance in MTB (Table 2).\textsuperscript{19}

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### Table 1 At-risk groups associated with higher rates of tuberculosis

<table>
<thead>
<tr>
<th>At risk group</th>
<th>Global prevalence**</th>
<th>Major mechanism contributing to susceptibility to MTB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human immunodeficiency virus\textsuperscript{1,3}</td>
<td>34 million</td>
<td>Immunosuppression of T cells by HIV activates latent MTB</td>
</tr>
<tr>
<td>Diabetes\textsuperscript{1,4}</td>
<td>180 million</td>
<td>Possibly related to reduced Interferon-(\alpha) and Interleukin-12 production along with a diminished T-cell response</td>
</tr>
<tr>
<td>Protein-calorie malnutrition\textsuperscript{7-9}</td>
<td>925 million</td>
<td>Reduction in thymus and lymphoid tissue development and maintenance Decreased antibody production</td>
</tr>
</tbody>
</table>

** Prevalence shown is the global prevalence of the chronic diseases.

Poor availability of drugs, geographic isolation of patients, lengthy and expensive treatment regimens, medication side effects and inappropriate diagnosis and drug prescription can reduce treatment completion rates, particularly in resource-poor countries.\textsuperscript{20} Premature cessation of treatment regimens creates a selection pressure that enables the overgrowth of drug-resistant strains, as evidenced by the high number of MDR-TB cases with a previous history of TB treatment. The current treatment regimen for drug-susceptible TB includes a minimum six months of uninterrupted therapy using combinations of four drugs: rifampicin, isoniazid, ethambutol and pyrazinamide (Table 3).\textsuperscript{21} Latent TB is treated with six to nine months of INH only.\textsuperscript{22} Therapy for MDR-TB is more complicated and involves at least 20 months of multi-drug treatment, while treatment for XDR-TB is individualised to the patient based upon susceptibility testing (Table 3).\textsuperscript{21,22,23}

Length of treatment and side effects from the medications often leads to non-completion of the course, with as few as 48% of MDR-TB patients successfully completing the treatment regimen.\textsuperscript{7}
Table 2: Mycobacterium tuberculosis gene mutations. Gene mutations that confer A) rifampicin resistance; B) isoniazid resistance; C) pyrazinamide resistance; D) ethambutol resistance.

<table>
<thead>
<tr>
<th>A) Mutation in rpoB gene</th>
<th>Location</th>
<th>Effect of mutation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRDR (codons 507-533)</td>
<td>Core region of rpoB surrounding RIF-binding pocket</td>
<td>Directly or indirectly affects RIF binding to the α-subunit</td>
<td>94% - 98%</td>
</tr>
<tr>
<td>Codon 146</td>
<td>Beneath RIF-binding pocket</td>
<td>Valine exchanged for phenylalanine</td>
<td>2.6% - 11%</td>
</tr>
<tr>
<td>Codon 572</td>
<td>Wall of RIF-binding pocket</td>
<td>Isoleucine exchanged for phenylalanine</td>
<td>2.6% - 11%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B) Mutated gene</th>
<th>Enzyme</th>
<th>Effect of mutation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>katG</td>
<td>Catalase-peroxidase</td>
<td>Expression of enzyme is reduced. This inhibits the formation of INH-NAD</td>
<td>47.1% - 96% of resistant strains, most commonly at codon 315</td>
</tr>
<tr>
<td>inhA</td>
<td>Enoyl-acyl carrier protein (ACP) reductase</td>
<td>Permits the production of mycolic acids via a poorly understood mechanism</td>
<td>31.3% of resistant samples</td>
</tr>
<tr>
<td>maba (inhA promoter)</td>
<td>NADPH-dependent beta-ketoacyl reductase</td>
<td>Increases the synthesis of enoyl-ACP reductase. This permits the production of mycolic acids</td>
<td>NK</td>
</tr>
<tr>
<td>ksaA</td>
<td>Beta-ketoacyl ACP synthase</td>
<td>Permits the production of mycolic acids via an unknown mechanism</td>
<td>NK</td>
</tr>
<tr>
<td>ahpC promoter</td>
<td>Alkyl hydroperoxidase</td>
<td>Associated with katG mutations. Increased expression of enzyme provides an antioxidant effect compensating for the lack of catalase activity induced by katG mutations</td>
<td>NK</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C) Mutated gene</th>
<th>Enzyme</th>
<th>Effect of mutation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>pncA</td>
<td>Pyrazinamidase/nicotinamidase</td>
<td>Expression of enzyme is reduced. This inhibits the formation of pyrazinoic acid.</td>
<td>72% to 97% of resistant strains</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D) Mutated gene</th>
<th>Enzyme</th>
<th>Effect of mutation</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>embB</td>
<td>Arabinofuranosyl transferase</td>
<td>Enzyme is unable to be blocked by ethambutol</td>
<td>44% - 69% of resistant strains have mutation at codon 306</td>
</tr>
<tr>
<td>embC</td>
<td>Arabinofuranosyl transferase</td>
<td>Enzyme is unable to be blocked by ethambutol</td>
<td>NK</td>
</tr>
</tbody>
</table>

RRDR – Rifampicin resistance-determining region; RIF – rifampicin; INH-NAD – active form of isoniazid prodrug; NK – not known

Table 3: Comparison of current treatment regimens for drug susceptible, latent, multi-drug resistant and extensively-drug resistant tuberculosis

<table>
<thead>
<tr>
<th>Drug susceptible TB</th>
<th>Latent TB</th>
<th>MDR-TB</th>
<th>XDR-TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs used to treat TB</td>
<td>Rifampicin, isoniazid, pyrazinamide and ethambutol</td>
<td>Isoniazid</td>
<td>Pyrazinamide, and at least one of each of: a) Fluoroquinolones b) Kanamycin/amikacin/ capreomycin/ viomycin c) Thioamides d) Cycloserine/teridizone</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>6-9 months total: 2 months with 4 drugs, plus at least 4 months with rifampicin and isoniazid</td>
<td>6-9 months</td>
<td>24 months total: 8 months with at least 5 drugs, at least 16 months of 4 effective drugs</td>
</tr>
<tr>
<td>Complications</td>
<td>Non-completion due to adverse effects, selecting for MDR/XDR organisms</td>
<td>Resistance to isoniazid develops quickly</td>
<td>Drugs are more toxic and more expensive</td>
</tr>
</tbody>
</table>

Rifampicin resistance

The first-line drug Rif is a bactericidal agent that inhibits protein synthesis in its targets (Figure 2A).24 Resistance to Rif in MTB is conferred by mutations in the rpoB gene encoding the α-subunit of the bacterial RNA polymerase (Table 2A). The majority of mutations are located within a 27-codon sequence in the centre of the rpoB gene, known as the rifampicin resistance-determining region (RRDR). More than 80 different mutations within this area have been determined through sequencing assays.25 Yam et al. found that all MTB samples shown to have RRDR mutations were resistant to Rif, based on standard antimicrobial susceptibility testing.26 The most common RRDR mutations observed across the literature occur at codons 531 and 526.25,27 Entire rpoB gene sequencing of clinical isolates from patients with recurring TB infection has identified another two resistance-producing rpoB gene mutations. These occur outside of the RRDR at codons 146 and 572. Monoresistance to Rif is rare in MTB and is paired with isoniazid resistance in more than 90% of isolates. This makes it an ideal marker for MDR-TB.26
at codon 315, which creates resistance by inhibiting the formation of active acid biosynthesis pathway.\textsuperscript{15,29} Mycolic acid is an essential component of INH-NAD discovered was enoyl-ACP reductase, an enzyme in the mycolic acid synthesis pathway. INH-NAD is thought to inhibit enoyl-ACP reductase by binding to it, thereby inducing a conformational change which prevents the natural substrate binding. However, in vitro studies have failed to show that INH-NAD binding is altered by mutations to inhA.\textsuperscript{31,34}

**Isoniazid resistance**

The exact mechanisms of INH activation, activity and resistance are unclear and remain the focus of current research. Isoniazid is a prodrug activated by a bifunctional catalase-peroxidase enzyme encoded in the M. tuberculosis gene inhA.\textsuperscript{15,26,27} Activation is hypothesized to occur via the reaction of a radical species with NAD+ to form INH-NAD. The first target for INH-NAD discovered was enoyl-ACP reductase, an enzyme in the mycolic acid biosynthesis pathway.\textsuperscript{15,29} Mycolic acid is an essential component of the mycobacterial cell wall; hence, inhibition of this pathway by INH-NAD leads to cell lysis and death (Figure 2B).\textsuperscript{29-31} More recently other targets for INH-NAD have been found, including beta-ketoacyl ACP synthase, another mycolic acid biosynthesis enzyme; and dihydrofolate reductase, an enzyme that catalyzes the reduction of folic acid, which is necessary for synthesis of nucleic acids, purines, pyrimidines and a number of amino acids.\textsuperscript{30}

Isoniazid resistance has been linked to multiple mutations within certain MTB genes, with some mutations resulting in strains that are more resistant than others (Table 2B).\textsuperscript{33,34,35} The most commonly reported mutation is in katG at codon 315, which creates resistance by inhibiting the formation of active INH-NAD.\textsuperscript{29,36} pncA mutations also occur frequently in resistant strains. inhA, along with mabA and kasA, are genes that encode other enzymes within the mycolic acid synthesis pathway. INH-NAD is thought to inhibit enoyl-ACP reductase by binding to it, thereby inducing a conformational change which prevents the natural substrate binding. However, in vitro studies have failed to show that INH-NAD binding is altered by mutations to inhA.\textsuperscript{31,34}

**Pyrazinamide resistance**

Pyrazinamide (PZA), another prodrug, is activated by the MTB enzyme pyrazinamide/nicotinamidase encoded in its pncA gene. The drug simultaneously inhibits both RNA and protein synthesis, though no specific cellular targets have been identified. Pyrazinoic acid (POA), the active form of the drug, becomes protonated in acidic environments and accumulates in the cell. As a result, the bacterial membrane potential is reduced and the transport of nutrients into the cell, including some amino acids and uracil, is prevented (Figure 2C).\textsuperscript{15,37}

Resistance to PZA occurs most frequently through mutations in the pncA gene (Table 2C). At least 28 different mutations have been found spread throughout this gene. These create a loss of pyrazinamidase/nicotinamidase activity thereby preventing the formation of POA. However, some resistant strains show no pncA mutations. One such strain has shown a mutation 11 nucleotides upstream of the pncA gene which is thought to be a regulatory area for the gene. Other strains are yet to have a resistance-inducing mutation identified.\textsuperscript{38}

**Ethambutol resistance**

Ethambutol (EMB) inhibits the synthesis of arabinogalactan, a component of the mycobacterial cell wall that anchors the mycolic acid layer to the inner peptidoglycan layer, and lipoarabinomannan (LAM), a mycobacterial plasma membrane component.\textsuperscript{15,39} The exact mechanism by which EMB inhibits the production of these components has not been confirmed, although it is thought to inhibit at least two arabinofuranosyl transferase enzymes which are involved in the polymerization of arabinan into arabinogalactan and LAM (Figure 2D).\textsuperscript{39} These enzymes are encoded by the embB and embC genes respectively.\textsuperscript{15,39}

Mutations in embB and occasionally embC have been linked to EMB resistance (Table 2D).\textsuperscript{15,40} Recently the relevance of the most common mutation in embB at nucleotide 306, has been questioned, as studies have shown that it also appears in some strains that are susceptible to EMB.\textsuperscript{41} A recent study found that some amino acids that are substituted in response to embB306 mutations create resistance while the MTB remains susceptible when other amino acids are substituted. Some resistant strains have also been found with no mutations in embB and are yet to have a cause for their resistance identified.\textsuperscript{15}

**Challenges**

**Current tuberculosis control strategies**

The directly-observed therapy short-term (DOTS) program is the recommended control strategy for TB endorsed by the WHO (Figure 3). The key aim of this program is to increase treatment completion rates and therefore prevent the development of drug-resistance.\textsuperscript{1,22} Successfully-implemented DOTS programs require methods for the effective detection of TB. Traditionally, diagnosis has required sputum smear microscopy and nucleic acid amplification diagnostics.\textsuperscript{25,26} However, the advent of biotechnology, assays involving DNA sequencing and polymerase chain reaction (PCR) have been developed in relation to TB diagnostics.\textsuperscript{25,26}

- Ensure long-term government support, particularly financial, for TB treatment
- Timely detection of cases via appropriate bacteriological methods
- Management of cases throughout their duration by a trained healthcare worker, particularly during the initial 2 months
- Supply of appropriate drugs throughout treatment
- Follow-up of cases using mandatory standardised reporting systems

**Figure 3** The five components of the Directly Observed Therapy Short-term (DOTS) program.
Detection of drug resistance by molecular assays

Assays using molecular techniques such as line probe assays (LPAs) and real-time PCR have been developed as diagnostic tools specifically identifying drug resistance. Such techniques are increasingly being used instead of conventional culture and drug-susceptibility tests due to their superior specificity and sensitivity, ease of use, and speed of detection.\(^1\)\(^4\)

The GeneType MTBDRplus line probe assay is a fast, strip test that screens sputum samples for MTB genomic DNA using a set of DNA probes. One evaluation of this LPA indicated high sensitivity and specificity in detecting resistance to RIF but not INH, and recommended its use in resource-poor settings, as it displays results within 5 hours.\(^4\) A second LPA, the INNO-LiPA Rif.TB assay, particularly identifies RIF resistance. Use of this assay, however, is limited by its narrow range of MDR-TB detection and suboptimal sensitivity.\(^4\)

The most popular molecular technique in MDR-TB diagnostics is the GeneXpert MTB/RIF assay, which uses real-time PCR to amplify the rifampicin resistance-determining region and probe it for common resistance-inducing mutations. The test requires a maximum of 2 hours to perform and minimal training required to carry out the procedure. Both of these factors have led to its increasingly widespread use.\(^4\)

Molecular tests to determine RIF-resistance are more common due to their typical encoding within the rpoB gene. This simplifies such tests and allows faster determination of MDR-TB, thereby reducing the spread and potential severity of disease amongst patients. The deficiency of assays for detecting INH-resistance needs to be further addressed in order to appropriately diagnose and treat patients and achieve elimination of MDR-TB globally.

Prevention of tuberculosis through vaccination

As with many diseases, vaccination against TB could theoretically limit the spread of the disease; however the current vaccine, Bacille-Calmette-Guerin (BCG), is often ineffective.\(^1\)\(^4\) The vaccine contains a live, attenuated form of Mycobacterium bovis and was first used in 1921. Its subsequent distribution and continued culture in various laboratories around the world has resulted in the formation of a number of different strains. The efficacy of the vaccine is reduced as some of the resulting strains do not express important proteins required to stimulate the host immune system and produce a robust T-cell immunity to TB. As a live vaccine, BCG cannot be administered to HIV-positive individuals to prevent TB infection. Furthermore, inappropriate storage and transport of the vaccine are also implicated in the variable efficacy of the live vaccine.\(^4\) Production of a more effective vaccine that requires less stringent cold chain conditions and may be administered to immunocompromised individuals is a challenge currently being addressed. New vaccine candidates that attempt to address these shortfalls are currently in clinical trials.

Development of new drugs to treat MDR and XDR-TB

Development of novel treatment options for resistant TB is a pressing issue. The desirable attributes of such drugs include: varied mechanisms of action that do not interact with other TB or HIV medications; efficacy against resistant organisms; reduced duration of treatment; and lower cost.\(^2\) Studies into the mechanisms by which resistance is produced may provide insights into additional drug targets.\(^3\)\(^4\)

In December 2012, the United States Food and Drug Administration approved bedaquiline, a drug that is in phase II of clinical trials, for use in TB treatments on an accelerated approval program. This was the first new TB treatment to be approved in more than 40 years.\(^1\) Clinical trials are currently being conducted on a number of drugs that are already approved for use in other infections, as well as new drugs developed in recent years (Table 4).\(^1\)\(^4\)\(^8\)\(^5\)

Table 4 Drugs currently in phase II and phase III of clinical trials for the treatment of tuberculosis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Trial name (Phase of trial)</th>
<th>Description</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifapentine</td>
<td>Inhibits RNA polymerase</td>
<td>RIFAQUIN (III)</td>
<td>Rifapentine and moxifloxacin used instead of RIF and INH. Treatment – 2 months of daily doses, followed by a further 2 months of twice-weekly doses or 4 months of once-weekly doses. Findings – The 6-month treatment was not inferior to standard treatment though the 4-month treatment was less effective.</td>
<td>Completed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBTC31 (III)</td>
<td>Aim – To determine if the use of rifapentine instead of RIF can reduce the treatment time required for drug-susceptible TB to 4 months.</td>
<td>Planning stages</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TBTC29X (II)</td>
<td>Compared different doses of rifapentine (10, 15 and 20 mg/kg/dose) used in combination with INH, ETH and PZA. Preliminary findings – culture-negative status was achieved in all participants after 8 weeks compared with 16 weeks for standard treatment.</td>
<td>Completed</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td>Inhibits DNA gyrase</td>
<td>CFLOTUB, NCT00216385 (III)</td>
<td>Aim – To determine if the use of gatifloxacin in combination with INH, RIF and PZA for 4 months is effective for TB treatment.</td>
<td>Completed. Results to be published in 2014</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Inhibits DNA gyrase</td>
<td>REMox (III)</td>
<td>Moxifloxacin was used instead of either INH or ETH and length of treatment reduced to 4 months for drug-susceptible TB.</td>
<td>Completed. Results to be published in 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td>STREAM (III)</td>
<td>Aim – To determine if the use of moxifloxacin in combination with ETH, PZA and clofazimine for 9 months is effective for MDR-TB treatment.</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Delamanid (CPG-67683)</td>
<td>Inhibits cell wall synthesis</td>
<td>NCT01424670 (III)</td>
<td>Aim – To determine if the use of delamanid in combination with other drugs can reduce the treatment time for MDR-TB to 6 months.</td>
<td>Recruitment complete. Results due in 2016</td>
</tr>
<tr>
<td>SQ109</td>
<td>Inhibits cell wall synthesis</td>
<td>MAMS-TB-01, NCT01785186 (II)</td>
<td>Aim – To investigate the efficacy of various combinations of SQ109, moxifloxacin, INH, RIF, PYR and ETH for 3 months followed by 14 weeks of RIF and INH.</td>
<td>Recruiting</td>
</tr>
<tr>
<td>Bedaquiline (TMC-207)</td>
<td>Inhibits ATP synthase</td>
<td>NC-003 (II)</td>
<td>Investigated the efficacy of various combinations of bedaquiline, PA-824, PZA and clofazimine, used for 14 days.</td>
<td>Completed. Results to be published in 2014</td>
</tr>
</tbody>
</table>
Implications for global health
While the overall incidence of TB has fallen over the last few years, MDR-TB, XDR-TB and, very recently, totally drug-resistant TB (TDR-TB) strains have developed. The emergence of these resistant strains poses a major threat to global TB control as their treatment is not only not currently possible. Subsequent investigation into the links between HIV, DM, malnutrition and TB is warranted. The possibility that these chronic diseases have a causal link with TB suggests that the threat of resistant TB may increase in the future, due to increasing frequencies of these risk factors.1,3 Future research may also find focus on identification of any further risk factors for TB. Investigations into resistance mechanisms will be required for advances in new drugs, vaccines and diagnostic tools. The development of globally-accessible methods of detection of MTB infection and treatment options, along with new drugs to treat resistant strains and an effective vaccine, are required to control the spread of this potentially lethal infection.

Acknowledgements
We thank Professor Natakrum Kethesan, Tahnee Bridson and Stephanie Kemp for critical appraisal of the manuscript. We would also like to thank Renée Sands and Alannah Woodhouse, for providing references.

Table 4 (cont)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Trial name (Phase of trial)</th>
<th>Description</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA-824</td>
<td>Inhibits cell wall synthesis</td>
<td>NC-002 (II)</td>
<td>Investigated the efficacy of an 8-week treatment with PA-824, moxifloxacin and PZA.</td>
<td>Completed. Results to be published in 2014</td>
</tr>
<tr>
<td>Sutezolid</td>
<td>Inhibits cell wall synthesis</td>
<td>MARVEL AS319 (II)</td>
<td>Aim – To investigate the efficacy of various combinations of sutezolid, bedaquiline, SQ-109, levofloxacin, clofazimine, PA-842 and PZA.</td>
<td>Planning stages</td>
</tr>
<tr>
<td>AZD5847</td>
<td>Inhibits 50S ribosomal subunit</td>
<td>NCT01156203 (II)</td>
<td>Investigated the efficacy of various concentrations of AZD5847 (500 mg, 800 mg or 1200 mg once or twice daily) used for 14 days.</td>
<td>Completed. Results to be published in 2014</td>
</tr>
</tbody>
</table>
UNUSUAL PRESENTATION OF A COMMON DISEASE: A CASE REPORT

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2Department of Medicine, UniKL Royal College of Medicine, Perak, Malaysia
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Abstract

Tuberculosis is a major public health problem in underdeveloped countries, with pulmonary presentation most common, and disseminated tuberculosis least common, in immunocompetent patients. We report a case of disseminated tuberculosis with marked neutrophilic leucocytosis, in an immunocompetent patient. Leucocytosis, usually of lymphocytic or monocytic origin, is rare in all presentations of tuberculosis.

Key words: Tuberculosis, disseminated tuberculosis, leucocytosis, immunocompetent

Introduction

Miliary tuberculosis (TB) is often a perplexing disease with diagnosis eluding experienced clinicians, due to a myriad of clinical presentations and atypical radiologic findings. Hence, mortality remains high despite available effective therapy. Miliary TB, traditionally considered a childhood disease, has recently been increasingly recognized in adults. This is due to the prevalence of immunosuppression related to acquired immunodeficiency syndrome (AIDS), therapies for various medical disorders including transplants, and chronic haemodialysis programmes.1 Amongst immunocompetent adults, miliary TB accounts for less than two percent of all TB cases and up to 20 percent of all extra-pulmonary TB cases.2-9 We report a case of disseminated tuberculosis in an immunocompetent patient where severe granulocytosis and increased serum alkaline phosphatase were dominating features.

Case report

A 16-year-old female was admitted to a district hospital following three weeks of low-grade fever, and two days of non-productive cough with haemoptysis. There were no other respiratory or relevant symptoms, and physical examination was unremarkable, apart from a BCG scar on the left arm. The chest X-ray was reported as normal. The full blood count revealed severe neutrophilic leucocytosis and normocytic anaemia, markedly high alkaline phosphatase with normal bilirubin level and minimally-elevated transaminases (Table); urinalysis was normal, as were serum electrolytes. Blood cultures were negative (x 3), and was submitted for AFB culture. The Mantoux test was negative. Serological tests for hepatitis B antigen, and hepatitis C, HIV and leptospirosis antibodies were negative. The blood film for malaria parasites was negative. Serum B12, folate and iron levels were non-contributory.

Hepatic ultrasound, to rule out liver abscess, suggested an ‘anterior abdominal wall abscess’ and a computed tomography (CT) scan was ordered but was not immediately available. The working diagnosis was intra-abdominal abscess with septicemia. Intravenous (IV) cefuroxime was given for one week, then changed to IV ceftriaxone with IV metronidazole added for one week. IV ciprofloxacin was then given alone for an additional week, and the temperature gradually normalized. However, the patient’s neurologic status deteriorated with headaches, obtundation, without nausea or nucheal rigidity, and ultimately generalized tonic-clonic seizures. She was transferred to a secondary level hospital, where her Glasgow Coma Scale was 6/15 (eye 2, motor 3, verbal 1). A vague, ill-defined mass was felt in the lower abdomen under and to the left of the umbilicus extending to the pelvic region, approximately 5 x 5 cm. She was transferred to ICU and treatment for TB was initiated when the CT thorax scan revealed small bilateral pleural effusions and multiple small nodules in the bases of both lungs (Figure). The brain CT scan showed hydrocephalus, indicating basal meningitis (Figure). Microscopy, culture and polymerase chain reaction assay for TB bacilli, indian ink preparation for cryptococci, and biochemistry and cellular studies of cerebrospinal fluid were requested.

<table>
<thead>
<tr>
<th>Primary hospital (before starting TB drugs)</th>
<th>Week 1, secondary hospital (TB drugs started)</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>Week 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte count (x 10⁹/L)</td>
<td>18.3</td>
<td>23.3</td>
<td>32</td>
<td>49.2</td>
<td>19</td>
<td>15.2</td>
<td>8.2</td>
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<tr>
<td>Neutrophils (%)</td>
<td>74</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basophils (%)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Band forms (%)</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metamyelocytes (%)</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B₁₂ (pmol/L, normal range 156-698)</td>
<td>781</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>509</td>
<td>99</td>
<td>321</td>
<td>310</td>
<td>283</td>
<td>343</td>
<td>356</td>
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<tr>
<td>Aspartate aminotransferase (IU/L)</td>
<td>109</td>
<td>1960</td>
<td>124</td>
<td>34</td>
<td>23</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>Alanine aminotransferase (IU/L)</td>
<td>60</td>
<td>501</td>
<td>254</td>
<td>36</td>
<td>32</td>
<td>33</td>
<td>32</td>
</tr>
</tbody>
</table>

Table. Haematology and blood biochemistry results before and after commencement of specific anti-TB treatment.
was consistent with reports of disseminated tuberculosis.\textsuperscript{10} Caseous tuberculosis. The combination of lung, liver and pelvic organ involvement (as indicated by high serum alkaline phosphatase), intestine, spleen and abdominal wall abscess. Multi-organ involvement of lungs, meninges, liver and pelvis were clues to disseminated hepatic involvement, and a liver biopsy may have established the diagnosis, thereby avoiding the need for the mini-

The CT scan of abdomen and pelvis (Figure) showed no focal lesion in the anterior abdominal wall. There was omental caking in the abdomen and pelvis, with ill-defined bowel wall. Both ovaries were enlarged with cystic lesions. Omental caking in the lower anterior abdomen was abutting the superior wall of urinary bladder, probably accounting for the mass noted on ultrasound. Small nodules suggestive of peritoneal deposits were seen and a right subdiaphragmatic soft tissue collection was noted. There were no hepatic focal lesions and there was a small amount of ascites.

In the subsequent week, the full blood count normalised except for anaemia, but she developed severe anti-TB drug-induced hepatitis, ventilator-associated pneumonia and septicemia in the fourth week. She was treated with appropriate antibiotics and anti-TB drugs were reintroduced by titration. Mycobacterium tuberculosis complex organisms were finally identified on sputum culture six weeks after admission to the primary hospital. A mini-
laparotomy demonstrated purulent and caseous material in the peritoneal cavity, and adhesions of the small intestine. Peritoneal biopsy showed typical TB granulomas. Ziehl-Neelsen stain for AFB was negative and no fungal necrosis on peritoneal histopathology was consistent with the patient not being immunosuppressed.\textsuperscript{11}

Peripheral blood changes resembling myeloid leukaemia and aplastic anaemia have long been associated with disseminated tuberculosis,\textsuperscript{12} and careful haematological studies are often necessary to exclude TB.\textsuperscript{13} Miliary TB in compromised hosts is often cryptic and rapidly progressive. A continued abnormal blood picture after initiation of anti-TB treatment requires investigation for hematologic malignancy.\textsuperscript{14}

Conclusion

Disseminated tuberculosis is often fatal if therapy is delayed, and anti-TB treatment initiated a month following admission improved the patient’s condition and corrected the hematologic picture within two weeks. Lessons from this case are that anti-TB treatment should be strongly considered in any patient with prolonged fever or pyrexia of unknown origin, especially in endemic regions with a susceptible individual. Timely institution of anti-TB drugs after first admission would have likely contained the infection, avoided tuberculous meningitis and the high cost of prolonged ICU admission. In this case, a thoracic CT scan following the negative chest X-ray should have been done, as pulmonary TB was a possibility. The high serum alkaline phosphatase out of proportion to transaminases, together with a high serum B\textsubscript{12} level, were clues to disseminated hepatic involvement, and a liver biopsy may have established the diagnosis, thereby avoiding the need for the mini-

Discussion

Pulmonary tuberculosis was considered in this patient, who presented with prolonged fever and cough with haemoptysis despite a normal chest X-ray, and negative sputum and Mantoux tests. Some anti-TB effect of anti-TB treatment, supported by miliary shadows in the bases of both lungs in the thorax CT, and the abdomen CT dispelled the notion of abdominal wall abscess. Multi-organ involvement of lungs, meninges, liver (as indicated by high serum alkaline phosphatase), intestine, spleen and pelvic organs on CT of the abdomen, fulfilled the definition of disseminated tuberculosis. The combination of lung, liver and pelvic organ involvement was consistent with reports of disseminated tuberculosis.\textsuperscript{10} Caseous tuberculosis is often fatal if therapy is delayed, and anti-TB treatment initiated a month following admission improved the patient’s condition and corrected the hematologic picture within two weeks. Lessons from this case are that anti-TB treatment should be strongly considered in any patient with prolonged fever or pyrexia of unknown origin, especially in endemic regions with a susceptible individual. Timely institution of anti-TB drugs after first admission would have likely contained the infection, avoided tuberculous meningitis and the high cost of prolonged ICU admission. In this case, a thoracic CT scan following the negative chest X-ray should have been done, as pulmonary TB was a possibility. The high serum alkaline phosphatase out of proportion to transaminases, together with a high serum B\textsubscript{12} level, were clues to disseminated hepatic involvement, and a liver biopsy may have established the diagnosis, thereby avoiding the need for the mini-

**References**


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9
PAEDIATRIC TUBERCULOSIS: CHILDREN UNSEEN

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Abstract

The global burden of paediatric tuberculosis (TB) remains largely unexamined. Complexities of screening and accurate diagnosis have hampered epidemiological efforts to describe this complex epidemic and as a result, targeted, TB-specific interventions have largely been unavailable to children with this disease. Efforts to improve diagnostic capacity in known high-burden regions have been largely ineffective, both as a consequence of technical difficulties and often endemic, coincidental poverty. New diagnostic tools are increasingly available; however, their utility within high-prevalence regions remains unclear. The objective of this study was to examine the burden of paediatric tuberculosis, in the context of a scarcity of accurate epidemiological data, related to ineffective screening and diagnostic capacity in high-burden countries.

Keywords: paediatric; tuberculosis; epidemiology; disease burden; diagnosis; MDR-TB

Background

Following the declaration by the World Health Organization (WHO) of a global TB emergency in 1993, a staggering volume of academic literature and public health policy has been dedicated to this complex issue. The adult manifestations of TB have unfortunately been the primary recipient of this attention, with paediatric TB seemingly neglected, or simply appearing as a sub-category of adult research, literature and interventions. Challenges of accurate diagnosis due to the predominantly paucibacillary nature of childhood TB, and the subsequent exclusion from targeted sputum-positive therapy programs, has essentially disassociated an estimated one in ten sufferers of this disease from the surfeit of contemporary TB management praxis. Consequently, surveillance and treatment efficacy data is scant for childhood TB, and treatment guidelines and medications are predominantly adult focused and formulated. Since children diagnosed with TB are generally representative of a newly-acquired infection, they provide a sentinel indication of local TB strains and drug resistance patterns. However, despite recent advances in both TB diagnosis and treatment, the utility of these new technologies remains relatively untested in this neglected population. A review of recent and relevant literature, examining the current burden of childhood TB and its drug-resistant manifestations follows. Concerns regarding the realities of ineffectual screening and diagnostic practices in high-burden countries (HBCs) are discussed, and two emerging diagnostic tools are examined, and their potential utility in such areas is explored.

Methods

COCHRANE and MEDlne databases were searched for papers discussing the epidemiological burden of paediatric tuberculosis, and traditional and innovative approaches to diagnosis of paediatric TB in HBCs. Papers were preferentially selected by relevance to paediatric disease in high-burden regions. Search terms were: paediatric; tuberculosis; multi-drug resistant tuberculosis; high-burden countries; diagnosis; poverty; epidemiology.

Results and discussion: the global burden and epidemiology of paediatric TB and multi-drug resistant TB (MDR-TB)

Tuberculosis (TB) remains a disease of global significance. In 2009, there were an estimated 9.4 million new cases of TB internationally – more than at any other time in history. Current modelling of the paediatric burden of TB estimates that between 10 and 20 per cent of cases are found amongst children, with a much higher prevalence estimated in areas lacking in basic TB screening and intervention programs. Mirroring adults, the majority of childhood cases are found in 22 high-burden countries, where high rates of transmission and a relatively young population base, coincide with pervasive poverty, domestic overcrowding and malnutrition. Current estimates of paediatric TB in high-burden countries (HBCs) have been reported in excess of 30 percent of all cases, with widely variable incidence rates, ranging from 60-600 per 100,000 annually. The absence of equitable access to TB screening, diagnostic and treatment initiatives for children living in these countries has hampered efforts to accurately define the global burden of this illness. The World Health Organization’s (WHO) flagship TB project, DOTS (Directly Observed Treatment Short Course), has been lauded as a public health success in the management and reduction of TB globally. Yet until 2006, only smear-positive cases were reported for children suspected of having TB by DOTS programs, ignoring the well-known paucibacillary nature of childhood TB and the associated poor sensitivity of sputum testing. The resultant scarcity of accurate surveillance data prohibits reliable estimates of TB’s contribution to overall child mortality rates.

With the emerging global epidemic of multi-drug resistant strains of TB (MDR-TB), the prevalence and impact of this complex illness remain unclear in paediatric demographics. Defined as resistance to two key first-line drugs, isoniazid and rifampin, MDR-TB adds layers of complexity to diagnostic and treatment regimens already laden with difficulty. Current efforts to identify and then address MDR-TB are progressing slowly, and screening and intervention coverage is sparse. Less than 5 per cent of new and previously-treated TB patients were screened for MDR-TB in 2010, and patients enrolled in treatment programs for MDR strains were equivalent to less than 16 per cent of the estimated cases worldwide of MDR-TB. Drug resistance in Mycobacterium tuberculosis bacilli is thought to develop from spontaneous gene mutation in the presence of inappropriate chemotherapy. In the absence of drug pressures, these mutations are believed to occur rarely – 1 in 10^5 - 10^6 bacilli; leading to the belief that the spontaneous development of MDR-TB genotypes is doubtful. In the instance of monotherapy, a small number of bacilli will be intrinsically resistant to that drug, and will subsequently be selected out. Exposure to a second anti-TB drug, either as a mono or poly-drug therapy, will similarly select for bacilli with dual drug-resistance characteristics. The result is MDR-TB; extensively drug-resistant (XDR) TB (MDR-TB with additional resistance to the fluoroquinolones and one of the injectable aminoglycosides); or totally drug-resistant TB (lacking a current and acceptable definition). It can be assumed then that the presence of MDR-TB and its relatives is the direct consequence of poorly-administered TB chemotherapy.

Paediatric TB is typically paucibacillary, and was not therefore considered to be a significant contributing factor to the dissemination of the disease or development and community proliferation of drug resistance. Children predominantly contract TB bacilli from adult contacts with active pulmonary disease (PTB), principally their parents, thus acquiring, if the parent is infected with a drug-resistant strain, a primary infection of drug-resistant TB. This provides a potentially useful population for community screening measures, enabling insight into transmission dynamics at a community level, as well as drug susceptibility and resistance patterns. Currently there is a significant lack of data relating to paediatric MDR-TB, with most publications emerging from the Western Cape Province in South Africa. Unsettlingly, longitudinal studies from high-burden areas, such as South Africa, reveal increasing prevalence of drug-resistant isolates from children. One such study reveals that between 6.9 and 15.1% of paediatric isolates were resistant to at least one anti-TB medication, and up to 6.7 percent were classifiable as MDR-TB. Another recent study from Johannesburg provided similar paediatric isolate resistance profiles (14.2% with any form of resistance; 8.8% with MDR-TB).
Real concern is beginning to emerge that children in high-risk countries will increasingly shoulder the burden of TB infection and its corollaries. In countries with a high prevalence of HIV infection, there has been a concerning and related increase in the incidence, and a decrease in the peak age prevalence, of diagnosed TB; subsequently, most cases are now found in young adults in these areas, who coincidentally are also often parents of young children.22 In 2007, the majority of smear-positive infections found in children were in Africa and South East Asia (SEA), with African counterparts. The characteristic paucibacillary nature of active and latent infection was suspected.31,32 Unfortunately, IGRAs share the same weakness as TSTs and IGRAs shared similar levels of accuracy when latent or active TB disease and to respond rapidly with appropriate chemotherapy and contact tracing. Inadequate diagnostic accuracy and the inability to identify drug-resistant strains is feeding the TB and MDR-TB crisis, placing further strain on already under-performing local and international health infrastructure.

In the absence of definitive diagnostic capabilities in HBCs, treatment initiation often relies on a triad of close contact with a known infectious patient; a positive tuberculin skin test (TST); and the presence of clinically-suspicious abnormalities on chest radiography.20 This clinical triad has obvious limitations of positive and negative predictive values, particularly in HBCs, where case detection and contact tracing is not widespread, and the majority of the population will have acquired TB during childhood to some degree and consequently be TST positive regardless of disease presence.27,28 Children meeting the triad’s criteria are often commenced on a course of non-fluoroquinolone antibiotics. Those children who do not respond to this initial therapy are presumed to have TB and are often commenced on a TB treatment regimen, typically in the absence of bacteriological confirmation.29 Unfortunately, chest radiography, a key pillar of diagnosis in such an algorithm, is particularly insensitive and unspecific. Chest X-ray findings are normal in a significant proportion of children with confirmed pulmonary TB, and perhaps more importantly, significant intra- and inter-observer variability, limits the utility and reliability of chest radiography as a diagnostic, ‘rule-in’ or ‘rule out’ measure.29

New diagnostic prospects

Two significant additions to the TB diagnostic cache have recently gained attention from the global public health community. Interferon-gamma release assays (IGRAs) and nucleic acid amplification tests (NAATs) have been commercially available for some time; however, recent evidence has given hope that their use may be indicated and useful in children.30 IGRAs are immune-based tests, which detect cellular immune response to past or recent sensitisation to mycobacterial antigens.30 Although IGRAs are unable to distinguish between current or historic disease, they do yield a very high specificity for Mycobacterium tuberculosis (MtB). Additionally IGRAs are reportedly able to distinguish between an exposure to Mycobacterium bovis, bacillus Calmette-Guérin infection (BCG vaccination), sensitisation caused by nontuberculous mycobacterial infection, and sensitisation caused by MtB infection.30 Currently, two IGRAs are commercially available: the ELISPOT-based T.SPOT.TB, and the ELISA-based QuantiFERON-TB-Gold test.30 In 2011, two large meta-analyses were published, which revealed that in children, TSTs and IGRAs shared similar levels of accuracy when latent or active TB infection was suspected.31,32 Unfortunately, IGRAs share the same weakness of low specificity in high-burden regions as TSTs, leading to an unacceptably high number of false-positives and therefore unnecessary provision of chemotherapy.23,24 This low specificity in high-prevalence countries has led the WHO to strongly recommend that IGRAs not be incorporated into TB screening initiatives in low and middle-income countries.30

In contrast, NAATs offer a more hopeful diagnostic avenue for children suspected of having TB in high-burden regions. They provide clinicians with a rapid and accurate test for detecting MtB, with some variants having the additional capacity to detect characteristic drug resistance.30 With an overall sensitivity in AFb microscopy-negative, culture-positive specimens of between 50 and 85%, and 95% in AFb-positive samples, and reported specificity in excess of 97%, the utility of such a test could be widespread.30 In an effort to address the increasingly obvious paediatric TB epidemic, the WHO updated its MDR-TB guidelines, advising that timely and accurate drug sensitivity testing (DST) be conducted, within 48 hours, for all children with confirmed TB prior to the commencement of chemotherapy.30 In order to achieve this, the guidelines have recommended the use of a rapid test that can identify resistance to isoniazid and rifampin in HBCs; currently the only NAAT commercially available that can achieve this target is Xpert-MTB/RIF.30

The question of whether the use of MTB/RIF testing will translate into improved diagnostic potential in HBCs remains unresolved. In 2011 a study
was published which examined the use of MTB/RIF testing in 1730 eligible patients in Peru, Azerbaijan, South Africa and India. The study attempted to examine the use of MTB/RIF as a means of detecting pulmonary TB and rifampin resistance in low-income regions. The results reported were very encouraging, with the assay identifying 97% of all patients with culture-confirmed TB, and greater than 90 per cent of AFB smear-negative specimens.

The potential function and utility of MTB/RIF testing in high-burden and resource-poor nations is unambiguous. However, requisite manufacturing costs, and despite concessionary pricing being mooted, the financial expenditure for such a test is far in excess of traditional microscopy outlays.

With simple and largely automated testing procedures, MTB/RIF is a potentially cost-effective, rapid, highly sensitive detection tool for both MTB bacilli and drug resistance, which has the potential to become a powerful diagnostic and epidemiological tool if made widely available. In an effort to harness the efficiencies of Xpert-MTB/RIF, the South African National Department of Health announced in early 2011 a nationwide programme that would equip all smear-microscopy laboratories with Xpert-MTB/RIF capacity by 2016. Meyer-Rath et al. compared the predicted cost of implementing this programme with current baseline annual screening and treatment costs. The predicted costing data was presented in conjunction with the anticipated increase in new incident cases if the programme was successful implemented. Meyer-Rath’s model anticipated a 30% increase in diagnoses if Xpert was available widely, at a cost of between USD 287 million and USD 316 million over the intervening period. If full Xpert coverage were to be sustained the total cost of South Africa’s TB diagnostic and treatment programme would increase by 46%.

Meyer-Rath is careful to point out a number of limitations in her costing analysis, particularly if cost escalation is the sole outcome being considered. Importantly, her model is unable to take into account the social and economic benefits of early and accurate diagnosis such as increased quality and duration of life. Secondly, the analysis is based on current diagnosis and treatment guidelines with the associated inefficiencies of repetitive testing and inappropriate treatment initiation. Meyer-Rath’s modelling does not consider the increased efficiencies and reduced financial expenditure that Xpert adoption would convey through improved accuracy and single, point-of-care testing.

New technologies such as Xpert-MTB/RIF hold great promise, yet their potential utility in low-income, high-prevalence regions remain largely untested. Widespread adoption of NAAT technologies will substantially increase the cost of TB diagnosis. It will also significantly increase the number of TB cases diagnosed, MDR-TB cases identified and patients initiating treatment. This improved accuracy will impose an increased burden on traditionally fragile public health systems. It remains to be seen whether global efforts to combat TB will invest in such technologies and support their utility within HBCs.

Conclusions

Despite significant international attention and investment in TB control, its childhood manifestation remains a silent and closed epidemic. Complexities of diagnosis in high-burden regions have rendered observational and epidemiological data superficial and inefficient, leaving children segregated from widely-heralded public health successes in TB mortality reductions. It seems clear that in order to successfully combat this pervasive disease, the relationship between poverty and TB must become a prominent and influential component of TB management practice.

References


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BURULI (BAIRNSDALE) ULCER IN A FARMER FROM NSW

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Abstract

Buruli ulcers are non-healing ulcers caused by Mycobacterium ulcerans. They are common causes of skin lesions in endemic parts of Australia and Africa. M. ulcerans can be acquired from exposure to contaminated soil, vegetation, aerosol inhalation, or mosquito bites near swamps or slow-flowing water in endemic areas. Appropriate sampling and histochemical testing is necessary for prompt and accurate diagnosis. Management usually involves antibiotic therapy with or without surgery. We describe a case of a farmer from rural NSW, who presented to a general practitioner with a non-healing, rapidly-expanding ulcer on his forearm, and was referred for biopsy. History revealed travel to an endemic south coastal area of Victoria and preceding skin trauma. The diagnosis of Buruli ulcer was made by histopathological examination with appropriate histochemistry, followed by confirmatory testing. This case highlights the importance of obtaining an adequate history, including history of travel, and use of appropriate histochemistry.

Keywords: Buruli ulcer, Bairnsdale ulcer, mycobacteria, Mycobacterium ulcerans

Introduction

Buruli ulcer is a non-healing ulcer caused by Mycobacterium ulcerans.1 The name is derived from Buruli (now Nakasongola) district in Congo, where a cohort of cases was first identified.2 The ulcer is often referred to as the Bairnsdale ulcer after the first published description of the disease, where the causative organism was isolated from patients living in Bairnsdale, Victoria, in 1948.3 The ulcer typically occurs in tropical and subtropical regions, and is endemic in the coastal areas of Victoria. Clustered cases have been identified in Bellarine,4 Mornington Peninsula,5 Gippsland, Phillip Island6 in Victoria, and Far North Queensland.7 Sporadic cases were reported in the Northern Territory,8 Capricorn Coast of southern Queensland,9 as well as single cases identified in Western Australia10 and New South Wales.11

Mycobacterium ulcerans is the third most common mycobacterial infection worldwide in immunocompetent patients, after M. tuberculosis and M. leprae.12 M. ulcerans may be acquired from exposure to contaminated soil, vegetation, or aerosol inhalation,13 particularly from aquatic environments such as swamps or slow-flowing water.1,2 It has also been detected in West African aquatic plants,14 insects, crustaceans, molluscs, and small fish.15,16 Mosquitoes have been implicated as a vector in the transmission in southeastern Australia,23 and mammals have been identified as reservoir hosts.15

M. ulcerans grows preferentially at 32-33°C and is associated with pre-ulcerative, ulcerative, and healing or scarring stages.24 The preulcerative stage is in the form of nodules, plaques or oedematous lesions that develop into painless ulcers with characteristic undermined edges3 (Fig. 1; from a different case). The ulcerative stage results from extensive coagulative necrosis of the skin and soft tissues, with formation of large ulcers, usually on the leg or arm, due to the production of mycolactone, a polyketide toxin.24 In immunocompetent individuals, M. ulcerans rarely causes systemic infections, but has been associated with bone lesions.24 Buruli ulcer is a neglected tropical infectious disease.

Case Study

A 51-year-old farmer from rural NSW presented to his general practitioner with a non-healing, rapidly-expanding ulcer on his left forearm. The ulcer had been present for over two months. The lesion was attributed to a spider bite, acquired whilst on a trip to the south coastal area of Victoria. The lesion started as a small nodule and progressed rapidly over two months with ulceration. The lesion was excised by a surgeon, and was submitted for histopathological examination. Routine microscopic examination (after haematoxylin and eosin staining) showed full thickness skin ulceration (Fig. 2) with surrounding coagulative and fat necrosis (Fig. 3). A poorly-formed granuloma was seen with Langhans-type giant cells (Fig. 4). Special histochemistry with Ziehl-Neelsen stains identified numerous acid-fast bacilli (Fig. 5). The acid-fast bacilli were identified by PCR as M. ulcerans. Treatment commenced, with combination of streptomycin and rifampicin for eight weeks.
combined with intramuscular streptomycin for eight weeks, or followed by clarithromycin for a further four weeks.\textsuperscript{23} Combination of rifampicin and clarithromycin, rifampicin alone, or rifampicin in combination with surgery have also been used.\textsuperscript{24} Preventive strategies against Buruli ulcer include using protective clothing and avoidance of insect bites, use of insect repellents, cleaning skin or wounds after soil exposure, and mosquito control.\textsuperscript{1}

**Conclusion**

Buruli ulcer can be a significant cause of morbidity in endemic regions such as coastal areas of Victoria and tropical-subtropical Queensland. M. ulcerans can easily be missed as a cause of non-healing ulcers without appropriate sampling and histochmetry. This case illustrates the importance of awareness of this skin infection in extensive, non-healing, non-tumoural skin lesions. A complete clinical history including the patient's lifestyle and travel history, with appropriate acid-fast staining of samples, needs to be done in any suspicious case with or without granulomatous inflammation.

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11. A complete clinical history, including the patient's lifestyle and travel to endemic areas, should be routine in lesions with or without non-healing granulomatous inflammation. A case of delayed diagnosis of M. ulcerans in a 60-year-old yacht rigger from Victoria resulted in a medicolegal case against a pathologist, who failed to carry out the appropriate special histochemistry,\textsuperscript{25} which was performed four months after the specimen was collected.

A complete clinical history, including the patient's lifestyle and travel to endemic areas, is essential when assessing a patient with a non-healing ulcer. People who regularly swim or wade through rivers,\textsuperscript{26,27} or those who farm near rivers in endemic areas\textsuperscript{28} are at increased risk of developing Buruli ulcer.\textsuperscript{29} Development of Buruli ulcer was almost always in people with mosquito bites on the lower legs or lower arms, and were halved with use of insect repellent, wearing of long trousers outdoors, and immediate washing of minor skin wounds.\textsuperscript{23}

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The incubation period for M. ulcerans is between 34 to 264 days, with an estimated mean incubation period of 135 days in Victoria.\textsuperscript{25} The patient in this case had a travel history to an endemic area in Victoria and skin trauma associated with a spider bite. Although there is no strong evidence for an association between spider bites and M. ulcerans,\textsuperscript{25} it may allow direct inoculation of the organism from contaminated soil or vegetation into the open bite wound.\textsuperscript{4}

The diagnosis of Buruli ulcer is based on demonstrating the acid-fast bacilli in smears from swabs or specimens from skin ulcers.\textsuperscript{30} Samples should be taken deep to the undermined edge of the ulcer using two dedicated cotton-tipped swabs, ensuring that material is visible on each swab. One swab should be submitted for PCR and the other for microscopy and culture. Fresh tissue biopsies and paraffin-embedded fixed tissue sections are also suitable for PCR. An incisional or excisional biopsy may be performed on high-risk patients with a suspicious plaque, necrotic patch, nodule or acute oedematous presentation.\textsuperscript{30}

Treatment of Buruli ulcer with antibiotics alone can lead to healing of ulcers without recurrence.\textsuperscript{1} Randomised, controlled trials have used rifampicin

**Discussion**

This case illustrates the importance of awareness of M. ulcerans infection in extensive, non-healing, non-tumoural skin lesions. Special histochemistry should be routine in lesions with or without non-healing granulomatous inflammation. A case of delayed diagnosis of M. ulcerans in a 60-year-old yacht rigger from Victoria resulted in a medicolegal case against a pathologist, who failed to carry out the appropriate special histochemistry,\textsuperscript{25} which was performed four months after the specimen was collected.

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Treatment of Buruli ulcer with antibiotics alone can lead to healing of ulcers without recurrence.\textsuperscript{1} Randomised, controlled trials have used rifampicin
Malaria is an enormous global burden, causing severe morbidity and mortality. Pregnant women are amongst the most vulnerable to the development of severe malaria caused by the multidrug-resistant protozoan parasite *Plasmodium falciparum*. Artemisinin derivatives are now widely used and highly effective in treating malaria. This paper explores the safety and efficacy of artemisinin administration as a treatment option for malaria during pregnancy. Clinical trials involving animal subjects have raised concerns over the safety of artemisinin administration in early gestation. At present artemisinins are only recommended by the World Health Organization as safe for the treatment of malaria during the second and third trimesters. However, it is concluded that the risk of developing artemisinin-induced toxicity is non-inferior to comparative antimalarials, and is far outweighed by the deleterious consequences of failing to adequately clear the parasite. Therefore, artemisinins should not be disregarded as a treatment option for first-trimester infections due to a lack of research evidence. Further research into the field of artemisinin use in treating malaria during pregnancy should be an immediate priority.

Keywords: malaria, artemisinin, pregnancy

**Introduction**

Malaria is one of the most prevalent and dangerous of all tropical diseases. It was estimated that in 2012, 207 million people were infected with malaria, resulting in an estimated 627 000 deaths. The global burden of malaria is carried largely by the developing world, with economic and environmental instability rendering sub-Saharan Africa one of the most susceptible of all developing regions. Pregnant women are among the most vulnerable to developing severe malaria and if left untreated, the infection can lead to severe morbidity and mortality of both the mother and the unborn child.

The World Health Organization (WHO) aims to reduce the overall incidence of malaria through the use of intermittent preventive treatment (IPT), insecticide-treated nets (ITN), and rapid clearing of parasitaemia.

The continued emergence of multidrug-resistant strains of *Plasmodium falciparum*, the parasite responsible for most severe malaria, has threatened the ability of health care workers to adequately treat this disease. So far the most highly-effective anti-malarial is artemisinin; however, there is limited knowledge about the maternal and foetal implications resulting from artemisinin exposure during pregnancy.

This review seeks to identify and evaluate the current literature on maternal and foetal response to artemisinin treatment, in order to extrapolate the risk-benefit ratio of artemisinin use in pregnancy.

**Background**

Malaria is a protozoan parasitic infection transmitted by the female anopheline mosquito. Five malaria parasite species, namely *P. vivax*, *P. malariae*, *P. ovale* the most recently identified *P. knowlesi*, and the most widely lethal, *P. falciparum*, have the ability to cause malaria in humans. *P. falciparum* is responsible for almost all cases of fatal malaria seen globally and is one of the most difficult to treat. The initial presentation of malaria is generally indistinguishable from many other tropical diseases, and includes abdominal symptoms, fevers and chills, malaise and myalgia, nausea, vomiting and anorexia. In most instances once appropriate treatment has commenced the disease is self-limiting, with no further evidence of organ dysfunction.

Pregnant women living in malaria-endemic regions experience fewer clinical symptoms when infected with the parasite. This is thought to be due to increased maternal immunity. Pregnant women affected by sporadic outbreaks, experience a greater incidence of clinical symptomatology. Epidemically-exposed women have higher parasitaemias in peripheral, cord and placental blood, resulting in greater risk of sequence into severe malaria. Regardless of the type of exposure, epidemic or endemic, pregnant women are physiologically more susceptible to adverse health complications.

If malaria during pregnancy is left untreated, rapid deterioration from uncomplicated to complicated malaria may ensue within hours, exposing the mother and foetus to severe risk. Infected mothers may experience a number of sequelae including cerebral malaria, metabolic acidosis, severe anaemia, acute pulmonary oedema, renal failure and hypoglycaemia, likely ending in death. Foetal risks range from foetal hypoxia, intrauterine growth retardation including congenital and skeletal malformation, spontaneous abortion and pre-term pregnancies. Malaria further increases the risk of low birth weight deliveries, which is a well-known precipitating factor for poor physical and cognitive development and increased disease susceptibility. It is also a significant contributing factor to high infant mortality rates in the developing world.

**Diagnosis**

Laboratory confirmation of malaria, in conjunction with suggestive signs and symptoms, is the positive identification of parasites during microscopy analysis. Placental histological examination postpartum has proven to be the most clinically accurate in determining levels of parasite burden. High placental parasite levels are believed to coincide with increased risk of maternal anaemia, resulting in an increased incidence of low birth weight deliveries. Maternal haematology is also highly indicative of foetal exposure levels, with cord microscopy proving the least conclusive. Given that the majority of malaria cases are seen in resource-poor environments with limited laboratory capabilities, confirmatory diagnostic measures such as these are simply not feasible.

In most instances health workers must rely solely on symptoms and the probability of exposure to guide treatment. Any degree of parasitic infection during pregnancy increases the probability of both maternal and foetal death and should be controlled aggressively in order to prevent deleterious outcomes for both mother and unborn child.

**Treatment options**

The management of malaria is multi-faceted and encompasses pre-and-post-exposure control methods. Preventive techniques such as the use of insecticide-treated mosquito nets, residual insecticide spraying, and the administration of intermittent preventive treatment (IPT) have proved beneficial in the fight against malaria. Appropriate pharmacological management has been challenged during recent years with the emergence of multidrug-resistant (MDR) strains of *P. falciparum*. Resistance to previously highly-effective antimalarials, exposes individuals to a greater threat of severe malaria and death.

During the last three decades artemisinins have proved highly successful in their ability to clear patients of *P. falciparum*. Scientific knowledge recognises the rapid parasitemia-clearing ability of artemisinins and the
highly successful post-treatment patient outcomes. However, most studies have investigated the use of artemisinins in non-pregnant patients, with limited research available pertaining to pregnant women. When animals are exposed to artemisinins, varying levels of embryotoxicity in early gestational periods have been identified in rodents, rabbits, frogs and monkeys.

To date there have been no reported cases in which pregnant women receiving artemisinin treatment have experienced any complications or adverse outcomes that could not be attributed to the underlying pathology of the disease. Furthermore, there is a growing body of compelling evidence to attest to the comparative superiority of artemisinin compounds over alternative antimalarials in pregnancy. Studies have shown that artemisinin-based combination therapies are well tolerated and exhibit fewer side-effects, such as hypoglycaemia and tinnitus, commonly seen with quinine administration. Artemisinin use has resulted in equivalent to faster parasitic clearance and symptom resolution rates and is associated with fewer foetal adverse events. Furthermore, these compounds have shown non-inferiority in regards to developmental milestones throughout gestation and the first year of life.

Due to the vulnerability associated with malaria during pregnancy and the lack of substantial evidence supporting artemisinin use in early gestation, the WHO currently only endorses the administration of artemisinins in second- and third-trimester pregnancies. First-trimester artemisinin treatment is recommended only when there is a threat of severe malaria and where no other option is available. In these instances, treatment should be commenced without delay and with whatever pharmacological means are available.

Artemisinin antimalarial activity

For more than two thousand years the Chinese have relied on the healing properties of the perennial herb *Artemisia annua* in the treatment of chills and fevers. In 1971 Chinese scientists were able to isolate the artemisin or qinghaosu compound from the leaf of the *A. annua* plant. Synthetic derivatives such as artemether and artemesate have since been formulated and are seen to be more active than the parent molecule. Compared to slower-acting antimalarials, artemisinins have a very broad specificity. The drug is capable of exterminating the malaria parasite throughout most stages of its life-cycle from the relatively inactive metabolic ring stage through to asexual reproduction and late schizont stages.

Artemisinins are known for their strong anti-plasmodial activity, eliminating parasitic biomass by 10⁴ or by approximately ninety-five percent within 48 hours of administration. Thus far, a dosage as low as 2 mg/kg has been noted to have dramatic parasitic clearance rates in humans. Unfortunately, when used mono-therapeutically in a short-course regimen, artemisinin compounds have displayed high recrudescence with failure rates of approximately eight percent in large cohort treatments. This is, however, thought to result from insufficient treatment durations as opposed to drug dosage levels or ineffectiveness. Due to inadequate management practices, countries of the Greater Mekong sub-region now experience increased susceptibility to the artemisinin class, highlighting the perpetual vulnerability of antimalarials in the fight against malaria. Regardless of this, to date artemisinins are still a more favourable alternative globally as compared to the widely-distributed quinine, which has a failure rate of up to thirty-three percent.

To prevent the development of resistance and recrudescence, it is advised that artemisinins be used jointly with a long-acting antimalarial in a regimen known as artemisinin-based combination therapy (ACT). Artemisinins have a short half-life of one hour, and when used in conjunction with a long-acting antimalarial such as mefloquine, ACTs show higher success rates with greater parasitic clearance and fewer episodes of recrudescence.

**Mechanism of action**

The pharmacokinetic properties of all artemisinins, regardless of varied synthesised or non-synthesised derivatives, are comparable to one another. Artemisinins require a one-electron transfer from a donor, such as ferrous iron (Fe²⁺), to activate an endoperoxide bridge resulting in either molecular alkalization or oxidation. It has therefore been elucidated that common effects would occur in all substances containing an endoperoxide bridge. Thus an artemisinin ‘class effect’ is likely during treatment, regardless of drug choice.

A clinical trial examining the developmental outcomes of rodent offspring post-artemisinin exposure has observed comparable results. It was found that equivalent exposure to four artemisinin compounds: artesunate, dihydroartemisinin (DHA), artemether and arteether, resulted in near-equivalent effects in terms of embryolethality and teratogenity, confirming the overall ‘class effect’ of embryotoxicity. Artemisinin-induced effects seen in animal trials range from anaemia and long bone curvature to gross skeletal malformation, cardiovascular and congenital abnormalities, to spontaneous abortion. It is important to note that, although the effects of artemisinins seem dire in these trials, the dosage used to induce such outcomes exceeds that which is required therapeutically in humans.

While research is slow to emerge regarding the mechanism and consequence of artemisinin toxicity during human pregnancy, growing knowledge surrounds the effects of exposure during the gestational period in animals. Recent scientific investigation involving animal subjects has revealed that the primary cellular target of artesunate is the embryonic erythroblast. Artemisinin-induced primitive cell destruction is considered to be responsible for embryotoxicity in early trimester rodent pregnancies, with the incidence of cell destruction preceding any indication of foetal malformation or lethality. Primitive cells, abundant in Fe²⁺, are targeted as donors in order to perpetuate the mechanism of action of artemisinin. As a consequence, vital elements in cells are depleted, leading to cell necrosis. While erythrocytic destruction is not the primary target of the drug, it is an unfortunate side-effect. Loss of primitive erythroblasts during the narrow window of organogenesis is thought to induce foetal hypoxia causing a reduction in oxygen-enriched haeme, leading to cell growth retardation and destruction.

**Bioavailability**

The variability of embryotoxicity is dependent on dose, route, timing and duration of exposure. A ‘window of sensitivity’ has been identified in rodents, whereby exposure to a single artesunate dose, between days ten and fourteen post-conception increased the prevalence of malformation and lethality. Although there is seemingly credible evidence to support the toxic ramifications of artemisinin administration during this time frame, studies have suggested that repeated doses over a greater period are more consequential than single-dose exposure during this period of sensitivity. Levels of sensitivity are also seen to be species-specific, with primates displaying an increased resilience to toxicity compared to the highly-sensitive rodent.

To date, researchers have supported the general safety of oral artemisinin use during the second and third trimester, as few studies have reported evidence of malformation or abortion. Late gestational stage embryolethality has, however, been identified in rodents intramuscularly dosed with high levels of artesunate. These results are more likely attributable to the varied levels of systemic involvement between oral and intramuscular administration coupled with excessive exposure levels. Consequently, the route of administration appears to play a vital role in determining the level of toxicity experienced. Oral drug administration is noted to have weaker absorptive properties compared to the intravenous mode of delivery. In a clinical trial examining bio-availability, it was found that in order to induce 100% post-implantation litter loss in pregnant rodents, an oral dose of ≥15 mg/kg/day was required. A much lower dose of 1.5 mg/kg/day was required when administered intravenously. Results indicate that although the family of artemisinins collectively exhibit a class effect, the route of administration in conjunction with dose and exposure periods plays a vital role in determining maternal and foetal outcomes.
Conclusion

Malaria has proven to be an enormous global burden, most severely affecting developing countries already suffering from economic and environmental hardships. The disease carries with it substantial morbidity and mortality, and the vulnerability of pregnancy enhances the risk of the mother developing severe malaria, greatly increasing the threat to the life of both the mother and unborn child.

Since inception in the marketplace, artemisinin derivatives have received great acclaim amongst scientists and in the international community, proving highly efficacious against the dangerous P. falciparum. Animal trials have enabled scientists to identify the synchronous effects of artemisinin dosing and embryonic toxicity during early gestation and organogenesis. Sensitivity levels vary between species, with rodents proving to be the most sensitive and primates more resistant, to experiencing artemisinin toxicity or lethality. Evidence suggests that artemisinin administered at extreme levels, far beyond what is required for parasitic clearance, have the potential to be lethal to the early developing embryo of animals. Whether or not similar levels of lethality would occur in humans is yet to be determined, although from the data currently available evaluating ACT versus alternative antimalarials including quinine, the results are indeed promising.

In order to fully elucidate the benefits and risks of artemisinin exposure in early pregnancy, more specifically-targeted research is required. To date, the risk of foetal complication from artemisinin exposure is non-inferior to that of current treatment methods. Future research focusing primarily on human and primate outcomes post-artemisinin exposure during early gestation is needed to guide policy and intervention programming.

References


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OBESITY IN DEVELOPING COUNTRIES: A REVIEW

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Introduction

Obesity is the global health challenge of the 21st century, with cardiovascular disease, for which obesity is one of the major risk factors, the leading cause of mortality globally in 2008.1 This is despite malaria and tuberculosis continuing unabated. AIDS in some settings increasing,2 and under- and overnutrition often occurring within the same community and even the same household.1,3 In this review, the extent of obesity and its consequences in developing nations will be illustrated, there is an overview of causal and contributory factors, and ways to address global obesity will be discussed.

Increasing overweight and obesity in the developing world

In January 2014, the UK-based Overseas Development Institute reported that one-third of all adults across the world, 1.46 billion people, are obese (BMI >30) or overweight (BMI >25), with most of these being in the developing world.2 The BMI, or body mass index, is measured by weight in kilograms divided by the square of height in metres and is used as an estimate of adiposity in populations. The greatest population prevalence of overweight and obesity continues to occur in high-income countries at 57% of adults >20 years old, compared with 37% in upper-middle income countries, 21% in lower-middle income countries and 15% in low-income countries.3 However, the greatest increase in obesity between 1980 and 2008 was in the developing world, with numbers almost quadrupling from 250 million to 904 million, whereas over the same period obesity prevalence increased by only 1.7 times in high-income countries.5 In 2008, global obesity prevalence was 9.8% in men and 13.8% in women, compared with 4.8% in men and 7.9% in women in 1980.6 The Pacific region is particularly affected by obesity, with the highest global rates recorded in several islands, e.g. Nauru, where 79% of adults were recorded as obese.7 In 2005, the World Health Organization reported that non-communicable diseases (NCD), a majority of which have an association with excess body adiposity, accounted for 60% of global mortality, with 72% occurring in developing countries.8 Another 2005 report by the WHO showed that NCDs, predominantly diabetes, killed twice as many people as infectious diseases, maternal perinatal complications and malnutrition combined.9 Diabetes is so intrinsically linked with obesity that the term ‘diabetes’ has been coined.10 The WHO estimated that 190 million people globally had type 2 diabetes in 2005, and that this was expected to double within one generation to 324 million by 2025.11 India and China have the highest numbers of type 2 diabetic patients in the world, with the prevalence of type 2 diabetes mellitus increasing from <3% in urban Indian adults in the 1970s to >12% in 2000 and >18% in 2006.12,13 However, in 2002 the WHO allocated only 3.5% of its total budget to NCDs.5 The Indonesian media reported that five NCDs drain most of the health budget of the government-run community programme, with 45% of these having obesity as a strong risk factor.14 The resulting increase in chronic disease rates will place a great strain on the health budgets of many nations, and could prevent economic progression and development, both in terms of monetary and manpower loss.15

The co-existence of both communicable and non-communicable disease has created a double burden of disease in many developing settings and in disadvantaged populations in developed settings.12,16 The idea that one can be “fat but fit” has taken hold in some commentaries of the obesity problem; however, this interpretation of health consequences of obesity is flawed, being drawn from laboratory-determined metabolic profiles and not on such clinical consequences as morbidity and mortality.16 A recent meta-analysis concluded that metabolically-healthy obese individuals had increased risk (relative risk [RR], 1.24; 95% CI, 1.02 to 1.55) for cardiovascular events and mortality, compared with metabolically healthy normal-weight individuals after 10 or more years of follow-up.17 Laboratory markers of complications of obesity often are not sensitive enough to detect early risk factors; for example, a fasting blood sugar level is less sensitive than a glucose tolerance test (GTT), which is less sensitive than a GTT with insulin levels or an HbA1C level at detecting chronic hyperglycaemia, insulin resistance and so-called pre-diabetes.18 The focus on metabolic syndrome ignores the consequences of obesity on other systems, such as musculoskeletal disorders, particularly osteoarthritis and gout, and on some cancers, namely endometrial, breast and colon cancer.19 Osteoarthritis is the fourth leading cause of disability worldwide.20 Obesity is the strongest risk factor for knee osteoarthritis (OA) and also is a risk factor for hip OA.21 In the USA, OA is second only to ischaemic heart disease as a cause of work disability in men over 50 years of age.22 Remoteness from facilities may exacerbate the problem; data from India, Bangladesh and Pakistan reveal more than double the prevalence of knee pain in rural settings (13.7%) versus urban settings (6.0%).23 Obesity is linked to nations transitioning economically and, consequently, nutritionally. A 2005 study using nationally-representative data collected between 1992 and 2000 in 36 developing countries found that overweight exceeded underweight amongst women of most developing countries.24 The median overweight to underweight ratio was 5.8 in urban and 2.1 in rural areas. On examining the data more carefully, evidence emerged of the so-called nutritional transition that developing countries face.17,25 Marked increase in prevalence of overweight was associated with an increasing gross national income (GNI) up to US $5000, after which prevalence levelled off.26 The disparity between rural and urban obesity declined as gross national income (GNI) and education levels increased. Higher educational attainment and urbanisation were associated with greater prevalence of obesity in low GNI countries but not in higher GNI countries, where rural and less educated women were as affected by obesity as urbanised or educated women.27 This propensity for obesity to go from afflicting the wealthier to affecting the poorer and less educated as nations become materially richer is called the nutritional transition, and is possibly explicable by the fact that women living in rural areas in high GNI countries have more ‘urbanised’ lifestyles, such as motorised transport and access to processed food, whereas those in less developed countries have to expend more energy in day-to-day life through lack of labour-saving technology.28 Another study of 39 low and middle income countries from 1991-2008 demonstrated the same phenomenon, with higher gross domestic product (GDP) countries in this survey experiencing faster growth rates in obesity in the lower-wealth groups.29 This has also been found in Australia, where obesity is concentrated amongst those living in areas of lower socioeconomic strata.20,30

Aboriginal populations in developed countries

In the Australian setting, the 2004-2005 National Aboriginal and Torres Strait Islander Health Survey (NATSIHS) reported higher rates of obesity (BMI >30) amongst Aboriginal Australians (29%) than non-Aboriginal Australians (17%).31 Obesity was particularly high in islanders, with 86% of Torres Strait Islanders living in the Torres Strait having BMIs of >25. The situation may be even worse than these figures imply, since the BMI can underestimate excess fat in Aboriginal individuals and populations. There are interracial differences in levels of body fat for a given BMI, and differences in risks for a given BMI. For example, Aboriginal Australians (AA) were found to have a lower BMI for a given waist-hip ratio (WHR), but higher biochemical risk factors for cardiovascular disease (raised lipids, CRP and homocysteine levels), than Aboriginal Canadians (AC).32 WHR was more strongly related than BMI to diabetes and cardiovascular risk and independently associated with glycosylated haemoglobin (HbA1C) in AA, whereas BMI was associated with raised HbA1C in AC. Aboriginal obesity, reflected in an elevated WHR, indicates visceral fat, which liberates fatty acids into the portal system directly, entering the liver and influencing the action of insulin action and synthesis of lipids, coagulation factors and inflammatory cytokines; this process may play a role in genesis of the metabolic syndrome and cardiovascular disease.33 WHR may be a more sensitive marker of metabolic sequelae of excess adiposity than BMI in other populations. The risk of type 2 diabetes is raised
in India if the BMI is above 23, whereas a BMI of up to 25 is considered low risk in Anglo-Celtic populations. Women in South Asia have higher rates of abdominal obesity (78%), as indicated by a WHR >0.8, than those in the rest of Asia (51%) and North-West Europe (67%).

Genes load the gun but environment pulls the trigger

Eliciting causes of obesity both between and within populations is a highly controversial area. Empiric evidence is lacking and observational studies are limited by biases inherent in such data. One commonly posed question is: 'Is obesity due to genes, or is it due to the environment?' My response after careful consideration is 'yes and yes'. In summary, 'genes load the gun and environment pulls the trigger'. Studies that elicit no difference in calorie (1 calorie = 4.2 kilojoules) intake or macronutrient ratios between thin and fat people within a population appear to strongly suggest the main aetiological factor is a genetic predisposition to weight gain, perhaps by mediating insulin and/or leptin resistance, hypothalamic 'set points' whereby appetite is regulated to maintain a set weight, or via gastrointestinal hormones that regulate appetite. A study compared carbohydrate, fat, and protein intake, as well as total energy intake, in 20-74 year old adults between the years 1971-1975 (I) and 2005-2006 (II), using data from the National Health and Nutrition Examination Survey (NHANES) to represent the US population. Interestingly, healthy weight men (mean 2551 +/- 37 calories) consumed a mean of 167 calories more than obese men (2386 +/- 41) in NHANES I and 190 more calories than the obese in NHANES II (2798 in normal weight men versus 2608 calories in obese men). Similarly, obese women ate somewhat fewer calories than normal weight women in both NHANES I (1446 versus 1626) and NHANES II (1787 versus 1809). Whilst intake seems similar in NHANES II in the obese compared to the normal weight, calories were lower if adjusted for body weight. Even given the self-reporting nature of dietary intake, which may have led to some overweight people recording a lower food intake due to the stigma of obesity implying gluttony, it is easy to understand why the public health messages discerned from such data may de-emphasise the role of calorie consumption in the development of obesity, and emphasise differences in physical activity patterns or genes, however, that would be an erroneous conclusion to draw. In Geoffrey Rose's seminal article from 1985, 'Sick Individuals and sick populations', a distinction was drawn between causes of disease in individual cases versus causes of disease incidence in populations. Case-control studies are not able to establish the causality in an individual of a ubiquitous exposure within a population. Such study designs require a heterogeneity of exposure within the studied population to demonstrate causality. In a ubiquitous/homogeneous exposure, genetic differences determine susceptibility to the universal exposure. An example is the effect of sunny climates on those genetically susceptible to melanoma: were sunlight levels alone assessed amongst sufferers and the unaffected within Australia, then its role may be obscured as the climate is universal to both; but its role is delineated when comparing rates of melanoma in sunny (Australia) versus grey (United Kingdom) climates.

In the NHANES surveys, those genetically susceptible were more likely to be obese within each time point even though they apparently ate less than those of normal weight. This may be because calorie consumption was above a certain threshold across all the weight ranges, such that the distribution of obesity was genetically determined. The comparison between two different time points, and thus two different populations with two heterogeneous exposures, however, is illuminating. Calorie intakes and percentage of calories from carbohydrates were uniformly higher in NHANES II compared to NHANES I, and there was a corresponding increase in rates of obesity in the population, highlighting the role of energy intake in development of overweight and obesity. Obesity levels doubled between the two survey time points from almost 12% to over 33%, with energy intake increasing across each weight range and both genders; men ate an average of 180 calories extra and women 200 calories extra between the two time points. Additionally, across all weight ranges and both genders, the percentage of calories as carbohydrate intake increased from 44% to almost 49%, whilst that of fat (36.6% to 33.7%) and protein (16.5% to 15.7%) declined. A study of calories consumed in over 600 women and over 150 men who kept off at least 13 kilograms for over 5 years revealed that an average calorie consumption to maintain weight loss was 1375 +/- 500 calories. This level is significantly less than the mean average consumption in the NHANES I and II surveys across all weight groups, and may indicate the level of caloric deficit needed to change obesity prevalence in a population. Physical activity patterns in the NHANES surveys were not reported. The high caloric intakes in the population generally may have provided the trigger for those individuals whose 'guns were loaded' genetically to develop obesity, whereas those without the necessary genetic susceptibility upon exposure to a high energy diet were protected. This suggests that, were there to be a famine in the land, then the rates of obesity would plummet due to an environmental shift in availability of energy, reducing energy supply to those genetically predisposed to weight gain. Thus, the environment modifies the degree and nature of certain exposures that are influenced in their consequences by genetic susceptibility.

Thrifty genotype

If indeed there are genetic influences in obesity, what are these and what environmental factors trigger them? Whilst there are no concrete answers, a couple of main theories predominate. Of the main postulated pathways discussed earlier (insulin resistance, leptin resistance, GIT hormones or hypothalamic signalling), the most commonly identified mechanism is that of induction and/or manifestation of insulin resistance. The 'thrifty genotype' hypothesis was first postulated in 1962 as a cause of type 2 diabetes mellitus (T2DM). It proposed that genetic susceptibility to T2DM is evidenced from birth, as this cohort has higher mean birth weights and mothers are often obese but may be of normal weight if fathers have T2DM, suggesting a genetic predisposition, independent of the uterine environment. This genetic susceptibility rendered the individual 'exceptionally efficient in the intake and/or utilization of food'. The mechanism postulated was high insulin levels, with resulting low blood sugar driving appetite and resulting in weight gain, now considered to be the manifestation of insulin receptor resistance.

Genetically-conferred insulin resistance was proposed to confer a selective advantage during times of famine, potentially via exaggerated insulin responses to hyperglycaemia inducing rebound hypoglycaemia, thus minimising post-prandial glycosuria and 'energy wastage' and, via glucose conversion to fat, inducing adiposity and ensuring survival during famine. Alternating famine and feast conditions characterised the traditional hunter-gatherer lifestyle of many civilisations, and it is proposed that they developed insulin resistance as an adaptation. These populations then have a greater tendency towards T2DM in environments of persistent easy access to food and calories, with modern farming and food storage removing the counterbalancing famines. The ability to survive long sea voyages with restricted access to food may have selected for thrifty genes in Polynesians who settled the South Sea Islands, explaining the high rates of 'diabesity' in these races. Those populations with hunter-gatherer lifestyles that have had to adapt rapidly to recent western lifestyles are particularly prone to obesity and diabetes, such as Aboriginal Australians, Indigenous Americans and Canadians, and Polynesians. A study of remote Aboriginal Australians who relied on hunting and gathering for food acquisition revealed that, whilst they were very lean (BMI 13-19), fasting insulin levels were higher than in both urbanised Aboriginal and Caucasian men with higher BMIs (average 21), despite lower levels of obesity and T2DM. Traditional pre-colonisation Aboriginal diets relied heavily on lean meats (e.g. kangaroo) and tropical seafoods, with alternate periods of food abundance ('feasts') and food paucity ('famine'). A protein-heavy diet would favour an insulin-resistant diathesis which promotes protein conversion into glucose (gluconeogenesis) but retention of sensitivity to the actions of insulin in promoting storage of energy as fat (hepatic lipogenesis), i.e. a state of 'selective insulin resistance'. Thus, insulin resistance may have evolved as a genetic advantage in the face of intermittent food scarcity, with the lower body weight and high levels...
of physical activity protecting against development of T2DM. This sets the population up for a rise in incidence of T2DM were there to be an increase in population BMI through environmental transformation affecting diet and activity patterns.

**Thrifty phenotype**

In contrast to the thrifty genotype hypothesis, the thrifty phenotype hypothesis, first raised in 1992 by Hales and Barker, suggests that foetal and early life malnutrition modifies genetic expression of pathways associated with energy metabolism and utilisation.42 These endocrinological consequences of intra-uterine and early life malnutrition are postulated to be mediated by genetic expression (phenotype) rather than genetic sequence change (genotype), otherwise known as the phenomenon of ‘epigenetics’.39 In 2001, in an updated theory, Hales and Barker highlighted the intergenerational effects of poor maternal nutrition such that the maternal endocrine environment in which a foetus incubates is influenced by her own developmental and nutritional history.36 According to the theory, maternal and consequently foetal/early postnatal under-nutrition impairs pancreatic function, leading to insulin receptor resistance and possibly a reduction in insulin secretion, and consequently deregulated blood sugar control in the growth-restricted newborn. In later life, metabolic complications of insulin resistance develop in the changed nutritional circumstances of abundance and plenty, namely ‘diabetes’ and dyslipidaemia.36,39 The diabetes epidemic has been associated with a rapid transitional nutrition. The association of reduced insulin secretion with T2DM has been less consistently replicated than that of insulin resistance and T2DM.40 It is debatable whether the thrifty phenotype contributes directly to the development of adult obesity or whether it simply increases the metabolic consequences of later life weight gain.2 Gene expression modification of the IgF1 gene via methyltransfer is one proposed mechanism that predisposes to adult obesity in growth-restricted newborns.41 Other proposed mechanisms for metabolic programming include exposure to excessive maternal cortisol, leptin, and insulin-modulating endocrine responses, or effects on appetite centres.42 A study of 4-year-old Indian boys demonstrated that, after adjusting for current size, glucose, insulin and insulin-like growth factor-1 concentrations were inversely related to birth weight.42,43 Studies of various human populations have shown that the phenotype changes in growth-restricted infants. Offspring born to women during the Dutch famine of WW2 were underweight but subsequently had an increased risk of glucose intolerance and obesity.44,45 Many other studies have demonstrated a link between low birth weight and insulin resistance, diabetes, obesity, high blood pressure, dyslipidaemia and cardiovascular disease.45-62 An environment of restricted intra-uterine nutrition followed by improved post-natal nutrition sets the scene for diabetes in the context of later life weight gain by predisposing to the metabolic syndrome diathesis.63 The developmental plasticity theory postulates that early growth is far more malleable than later growth, whereby from late infancy onwards nutritional supply affects rate of development rather than final size.40 Mouse studies reveal that these epigenetic changes are further modified by immediate post-natal nutrition: IUGR mice that had fast postnatal catch-up growth were more prone to obesity and diabetes development than those mice whose catch-up growth was delayed by nutritional restriction, with concomitant differences in IgF1 levels, indicating environmental modification of genetic expression.39 Likewise, the cohort of 4-year-olds described above were evaluated at 8 years of age, and growth velocity of height, weight and other growth parameters from 4 to 8 years of age was a stronger predictor of insulin resistance and CVD risk factors than the absolute measurements at 8 years of age.40 Of the rapid growers, those born underweight or to short parents carried the most adipose tissue. This phenomenon has clear implications for populations undergoing a nutritional transition, such that economic changes from poor food security to food abundance within one generation will impact on national incidence rates of diabetes and cardiovascular disease, as malnourished infants gain weight in adulthood. India is a case in point. Whilst adult Indians have a propensity to abdominal obesity and an escalating epidemic of T2DM, Indian babies are among the lightest in the world.64,65 Mothers (especially in rural India) are small and undernourished with deficiencies in iron and other nutrients.64 A comparison of 632 live-born singleton infants in Pune, India versus 668 normal live-born singleton babies born in Southampton was conducted.64 Indian mothers were younger and smaller and ate 500 fewer calories a day, with a greater proportion coming from carbohydrates (72% versus 50%). Adjusting for gestation, birth-weight, placental weight, neonatal head circumference and mid-upper arm circumpferences (MUAC) of the Indian babies were reduced in proportion to smaller maternal size. Reduction in abdominal circumference reflected reduced visceral size, MUAC reflected muscle mass, and subscapular thickness reflected adiposity, particularly that which is centrally distributed. Abdominal circumference in Indian babies was reduced out of proportion to differences in maternal size. Length was relatively spared and subscapular skinfold thickness markedly spared.65 The smallest babies in each group had the most relative fat sparing. Head circumference was reduced only in proportion to maternal size, reflecting the greater biological priority of brain preservation over that of viscera. Fat has an advantage in providing energy stores, reserves for brain growth in early infancy, and insulation, and potentially promoting mother-child bonding and feeding by conferring greater attractiveness to the baby.64 Small babies with preserved fat stores are sometimes termed ‘thin-fat’ babies.64,65 The authors suggested that the reduced muscle mass (MUAC) could compound insulin resistance and promote obesity by reducing motor endurance and physical activity, whilst the reduced abdominal visceral sizes could impair pancreatic beta cell development and insulin secretion and impaired renal salt handling with cardiovascular sequelae.60 These adaptations to poor energy supply may promote efficient energy utilisation and storage during early life, but are also considered by some to be a ‘predictive adaptive response’ whereby the metabolic skewing persists as the body anticipates that conditions of starvation will continue into adulthood. However, a counter-argument to this adaptation hypothesis is the fact that the greatest degree of insulin resistance develops when the energy supply is improving and the requirement for energy efficiency is at its lowest. This mismatch between early and later life nutritional environments results in a maladaptive state and consequent metabolic disease.41,63,65 Complicating the picture, associations between birth weight and late obesity are inconsistent between populations and appear to be environmentally dependent.67 A South Indian study revealed that T2DM at age 45 years was associated more with shorter birth length and ponderal index (weight/height4) than birth weight, and was more marked in offspring of heavier mothers.66 Indian babies from urban areas are heavier than rural babies (mean weight approx. 2.9 and 2.6 kg, respectively) but have a greater than 5-fold increased susceptibility to diabetes, probably because later life inputs such as diet and physical activity moderate early life responses.63 Indian investigators have demonstrated that small and large babies at birth are at risk of later insulin resistance, with large babies more likely to have overweight parents.67 Both small and large babies may have a relatively higher ratio of fat to lean tissue than normal weight babies, which may be the common factor predisposing to insulin resistance. A prospective study of Aboriginal Australians demonstrated that higher current weight and higher birth weight, rather than foetal growth restriction, were associated with insulin resistance.68 However, postnataal nutritional restriction and slow postnatal catch-up growth may have modified the epigenetic effects of IUGR. Alternatively, the metabolic manifestations may not occur until adulthood, when prevalence of overweight and obesity increases. Similarly, amongst Guatemalan young adults aged 20-29 years, BMI and high birth weight were more strongly associated with variances in blood glucose levels; however, the population was lean, with an average BMI of 22.1 for men and 23.6 for women, and with the onset of middle age and beyond as weight increases, metabolic sequelae of IUGR may manifest.69 However, in middle-aged men from Newcastle, UK current body composition, rather than birth weight, was associated with either insulin sensitivity and fasting or post-challenge glucose levels.70

**Environmental factors**

If the genetic and/or epigenetic propensity to obesity and its metabolic complications are modified by environmental triggers, what are the necessary conditions for their manifestation? With obesity globally doubling in the last 35 years, attention has turned to changes in social, economic, political and cultural conditions that are potentially influencing and shaping the nutritional environment. If weight is a product of the balance between energy intake and
energy expended, then are changes in the amount of daily energy expended, particularly the greater contribution of energy burnt during the activities of daily living, so called non-exercise activity thermogenesis (NEAT), over structured exercise, critical? Or are changes in dietary patterns primarily responsible? And which of these changes or combinations of changes can be held accountable for changes in prevalence of overweight and obesity? Which are reversible? Is reverting to traditional lifestyles either effective or tenable?

Globalisation and colonisation: changes in physical activity

The WHO reports a decrease in global activity levels and considers physical inactivity responsible for up to 10% of all non-communicable diseases and up to 30% of cardiovascular disease. 7,25 It can be empirically observed that modernisation, urbanisation and westernisation have changed the effort and activity required in everyday life of many in developing countries. 7,25 Globalisation describes the increasing interdependence of different national economies, with multinational companies outsourcing some of their processes offshore to save labour costs and avoid local regulations. This is allowing previously impoverished residents of developing counties to earn more income than they ever have, moving into urban centres to chase employment, and changing national economies from rural subsistence farming to service and manufacturing. 7,25 The risk: benefit balance of these developments is debatable, given the unregulated conditions of workers resulting in exploitative, and at times fatal, practices. 26 Nonetheless, many residents, particularly women, have increased economic power enabling them to become consumers. 7,27 According to the London-based Legatum Institute, Bangladesh is now economically trumping India in markers of health, wealth, education and security. 7,28 Many previous subsistence farmers, particularly women, are now employed in industry, which makes up 28% of the Bangladeshi work force, with Bangladesh second only to China as an exporter of apparel. In contrast, India has 19% of its workforce in industry, with new sectors in information technology and service provision opening up in the last 20 years. 7,29 These differences may be responsible for gains in child health, with child mortality, which was 20% lower in India than its neighbour in 1990, currently 25% lower in Bangladesh, with anaemia in school-aged children lower in Bangladesh (47%) compared to India (74%). With women economically enabled, health and education of children improves, but in developed settings this is coupled with less time to prepare food at home and a greater reliance on processed or restaurant meals. 29

Globalisation and colonisation: changes in diet

There has been a global increase in the average dietary energy available from 2,190 calories per capita per day (cal/cap/day) in 1961 to 2,830 cal/cap/day in 2009. 3 There are regional differences, with food energy per capita rising by 90% in China versus 19% in India. 5 Most of the increase in energy supply in northern and western Africa (<2000 calories in 1961 versus 3100 calories in 2009) was accounted for by increases in vegetable-sourced food, as opposed to animal sources, with limited change overall in East and Central African countries. In contrast, animal-sourced food supply increased 8-fold in China over this period. 3

Generally, as agrarian economies modernise, urbanise and globalise, the diets shift from minimally processed grains and starchy staples, with high fibre levels and inherently low glycaemic loads, to more animal produce, oils, fat and sugar, with the starch components refined and processed. 30 Malaise, milk and legumes were traditional staples in Africa, as were legumes and rice in India. 11,31 Since the 1990s, Indians have greatly increased consumption of animal products, and the traditional unprocessed starches have been replaced by wheat, starch root vegetables, sugars, vegetable oils, and fruit. 30 Traditional pre-colonial food sources in India were mainly dairy products; since World War II, vegetable seed processing has enabled a cheap and plentiful supply of vegetable oils, which have been readily taken up across Asia. 38

In contrast to traditional agrarian societies, hunter-gatherer societies had a protein-heavy diet. Pre-colonial Australian Aboriginals relied heavily on meat and fish, supplemented with fibrous tubers, fruits and nuts. 39 Early reports indicated that they were lean and fit, a state which persisted in the 20th century amongst remote Aboriginal communities who consumed a traditional diet. 30,31 These low-energy, low-carbohydrate, moderate-fat and high-protein diets contrast with modern western diets, which are high in calories, refined carbohydrates, sugars and fats. 39 During a seven-week trial, Aboriginal men (n=5) and women (n=5) with T2DM, and non-diabetic men (n=2) and women (n=2) were placed on a traditional diet heavy in kangaroo and fish. This resulted in 50-80% of energy intake being from protein, 20-40% from fat, and <5%-33% carbohydrates, the variability arising from the diversity of diets consumed over the 10 weeks, from inland to nomadic to coastal. 32 Total calories were 1200 per day. There was recorded weight loss of 3-12 kg amongst the diabetic subjects, almost halving of fasting blood sugars (mean 11.6 mmol/L to 6.6 mmol/L), halving of plasma insulin, and reductions in triglyceride measurements. In contrast, nutritional data collected from a central Australian Aboriginal community before and after a community-based nutrition awareness and healthy lifestyle program, from 1988-1990, showed carbohydrates increasing from 49% (22% starches and 27% sugars) to 54% (30% starches and 24% sugars) of energy intake, fat dropping from 40% to 33%, and protein increasing from 11% to 13%. Overall across all subjects, obesity increased from 23% to 37%, and diabetes from 12% to 21%. 32 A low-calorie intake of 1200 per day in the traditional diet may have been sustainable given the satiating properties of high protein, while low carbohydrate diets lead to lower overall calories than higher carbohydrate diets. 38 There is growing popularity over the last two decades of higher fat, higher protein and lower carbohydrate diets, with the latest iteration being the ‘Paleolithic diet’ designed to purportedly reflect the...
The benefits of a diet based on high fibre and high quality carbohydrates on health and weight was demonstrated in a study of Pima Indians in the USA, historically a hunter-gatherer society with a diet based on wild meats and fibrous carbohydrates. The benefits of a diet based on high fibre and high quality carbohydrates on health and weight was demonstrated in a study of Pima Indians in the USA, historically a hunter-gatherer society with a diet based on wild meats and fibrous carbohydrates. Whilst hunting is no longer practiced routinely, traditional Pima diets still contain many low-glycaemic, high-fibre carbohydrates. One hundred and sixty-five Pima Indian adults were followed up for 6 years and comparisons made between those who identified a traditional Pima diet, those who identified an 'Anglo' diet and those who said their diet was mixed. The study described the traditional diet being high in fibrous legumes and fruit as well as corn-based products: whether these were based on traditional low-glycaemic maize versus modern higher sugar, higher glycaemic corn varieties was not stated. The Anglo diet was simply described as the standard American diet. Levels of physical activity were higher in the traditional group but this was not statistically significant. Among women, complex carbohydrates, fibre and vegetable were significantly higher in the traditional diet group than in the Anglo diet group, and the values for the mixed diet group were intermediate. There were no differences in fat and protein contents of the 3 diets. Amongst men there was a tendency for levels of complex carbohydrates to be lower in the Anglo group. The effects on health of a modern diet were apparent by the fact that the incidence of diabetes in the Indian, mixed, and Anglo dietary groups were 23, 35, and 63 cases per 1,000 person-years, respectively, with the risk of developing diabetes in Anglo diet subjects being 3 times as high as that of Indian diet subjects. This indicates that components of traditional diets can be retained for the health of people from these cultures, without requiring full reversion to ancestral diets.

Socio-cultural changes

Social factors which influence diet include human physiological needs; food affordability; preferences formed by culture, media and trends; social changes in work patterns and gender roles; and globalisation influencing trade and public policy. With modern farming and food processing techniques, as well as efficiencies in food transport and storage, costs of food have been falling drastically over the last century. This is in the context of rising incomes, influenced in part by globalisation. It must be recognised that many remain too impoverished to afford a life-sustaining diet. However, higher incomes, as experienced by many in transitioning developing countries, are associated with a switch from relatively low-cost starchy staples to animal foods, fats and sugars. Greater access to manufactured foods and their advertising drives the process. Soft drinks are well recognised to be positively associated with childhood and adult obesity. An analysis of 75 countries revealed that consumption of soft drinks increased from 25 litres per person per year in 1997 to 43 litres in 2010, with a positive association demonstrated between soft drinks and 'diabetes'. Mexico, a middle-income country, has higher rates of overweight and obesity than USA, at 70% versus 69%. As well as replacement of a traditional diet high in legumes with a diet heavy in processed, refined starches, oil, sugar and meat, Mexico has the highest global consumption of dietary soft drinks in the world, at 146 litres of Coca-Cola per capita per year, and up to 850 litres per adult per year or over 2 litres each adult per day in the Chiapas region, which has a high indigenous population and is impoverished. The 2000-2006 Mexican president, Vincente Fox, was concurrently the supervisor of Coca-Cola's operations in Mexico, where he oversaw its rise to become the most-consumed beverage in the land, with Mexicans spending 14 billion annually on Coca-Cola purchases. Mexico has the largest Coca-Cola bottling facility in the world. Extra-large half-litre bottles of 'Coke' are only available in Chiapas, where school halls are branded with the Coca-Cola logo, and are handed out by volunteers for free at school events. Signs welcoming visitors in the area are sponsored and branded by Coca-Cola, and billboards are translated into the local dialect. Pricing is lower than in other parts of the country to reflect regional affordability. Coca-Cola has even replaced traditional Mayan beverages for ceremonial ritualistic use. Coca-Cola-backed television networks reportedly refuse to air warnings against excessive soft drink consumption. The UN food spokesman Oliver de Schutter attributes both the change in diet and the greatly increased soft drink consumption in Mexico to the signing of the 1994 North American Free Trade Act, with food imports soaring and Coca-Cola consumption doubling in the succeeding decade. Overweight and obesity in adult women doubled...
from 31% in 1988 to 59% in 1999, with T2DM, ischaemic heart disease and hypertension increasing by 60%. Compared with 1984, soft drink purchases increased by one-third, whereas purchases of meat dropped by almost one-fifth, dairy products by over a quarter and fruit and vegetables by almost one-third. Whilst observational data is prone to ecological fallacy whereby unrelated secular trends are inferred to have a causal association, the theory that globalisation of food supply has been central to the increase in obesity in Mexico fits with other observational data linking soft drinks to obesity. Coca-Cola has responded to criticism by sponsoring sports teams and emphasising the importance of exercise on its website, as well as offering recipes for family meals, but there is no appeal to consume its products.

Obesity: the future

If the current state of global obesity goes unabated, nations will be crippled by the swelling of healthcare costs, loss of productivity, and reduced life expectancy and quality of life of its citizens. As is the case for aetiology of obesity, there is a paucity of evidence on effective solutions to global obesity. A sense that we have lost control of the obesogenic environment, plus a misunderstanding of the causes of obesity, such that genetics rather than environment is considered the driving factor, is behind the development and large-scale rolling-out of both new appetite-suppressant medications and greatly increased access to government-funded bariatric surgery.

WHO conceded that education alone, whilst important, is unlikely to be solely adequate. They recommended cross-sector strategies, such as governments bringing public health and consumer protection ministries together, as has been proposed by the European Union. Acknowledging the role of globalisation, they have proposed considering modifying the World Trade Organisation’s free trade policy to prevent marketing and ‘dumping of unhealthy foods’ deemed undesirable in developed countries into developing ones. Rather, the WHO proposed that globalisation be leveraged to find solutions to the growing problem, through sharing of knowledge, research and innovation. An example cited is genetically modifying the starch in rice from high amylpectin content to high amylose to reduce its glycaemic index, as has developed for barley. Sharing of such technology between industries could impact the health of the two billion people for whom rice is a staple.

However, the change in texture may make the product unacceptable in some areas, and glycaemic index alone may not be the best measure of a food product’s nutritional profile. The GI of basmati (long-grain, high-amyllose) rice is 43 and that of carrots is 80. However, the GI of a typical 150 g serving of rice is 18, whereas that of an 80 g serving of raw carrots is 6. Focusing on quality of carbohydrates and ignoring quantity is likely to fail. On the other hand, banning trans-fats in food production in the North America and parts of Western Europe was successful in that it did not change the subjective taste or affordability of food and appears to have improved lipid profile in the USA and potentially reduced trans-fat-associated heart disease in Costa Rica. Through a combination of restrictions on advertising and sales, controls on use in public spaces, and significantly through application of taxes, there has been significant progress on alcohol and tobacco overuse and abuse. Subsidies have not always had a health agenda but rather an economic or even political one. However, taxing foods to reduce obesity is not without its pitfalls. In 2011 Denmark introduced a tax on foods containing more unhealthy fats. In 2011 Denmark, Finland and the USA found no significant changes in obesity rates, although there was a reduction in cost of food, a reduction in obesity rates, and a decrease in soft drink consumption. It remains to be seen whether this will halt or reverse the current alarming trend in obesity rates or whether the ‘horse has bolted’. WHO proposed that education alone, whilst important, is unlikely to be solely adequate. They recommended cross-sector strategies, such as governments bringing public health and consumer protection ministries together, as has been proposed by the European Union. Acknowledging the role of globalisation, they have proposed considering modifying the World Trade Organisation’s free trade policy to prevent marketing and ‘dumping of unhealthy foods’ deemed undesirable in developed countries into developing ones. Rather, the WHO proposed that globalisation be leveraged to find solutions to the growing problem, through sharing of knowledge, research and innovation. An example cited is genetically modifying the starch in rice from high amylpectin content to high amylose to reduce its glycaemic index, as has developed for barley. Sharing of such technology between industries could impact the health of the two billion people for whom rice is a staple. However, the change in texture may make the product unacceptable in some areas, and glycaemic index alone may not be the best measure of a food product’s nutritional profile. The GI of basmati (long-grain, high-amyllose) rice is 43 and that of carrots is 80. However, the GI of a typical 150 g serving of rice is 18, whereas that of an 80 g serving of raw carrots is 6. Focusing on quality of carbohydrates and ignoring quantity is likely to fail. On the other hand, banning trans-fats in food production in the North America and parts of Western Europe was successful in that it did not change the subjective taste or affordability of food and appears to have improved lipid profile in the USA and potentially reduced trans-fat-associated heart disease in Costa Rica.

Through a combination of restrictions on advertising and sales, controls on use in public spaces, and significantly through application of taxes, there has been significant progress on alcohol and tobacco overuse and abuse. Subsidies have not always had a health agenda but rather an economic or even political one. However, taxing foods to reduce obesity is not without its pitfalls. In 2011 Denmark introduced a tax on foods containing more than 23% saturated fat, based on a landmark seven countries study that causally linked heart disease to serum cholesterol levels, which were in turn attributed to saturated fat intake. A recent BMJ article summarised the growing scientific challenge to these findings, claiming that the original data were misinterpreted, that controlling for levels of carbohydrates did not occur, and that newer cohort studies showed no causal link between saturated fat and cardiovascular disease. The author proposed that saturated fat in fact was protective against cardiovascular disease and diabetes. The repeal of the Danish ‘fat tax’ less than a year after its introduction, however, was not for this reason but because of its unpopularity with Danes and pressure from the food industry. This result could have been anticipated from a 2010 study in 9 European countries and the United Kingdom, which found that food taxes and subsidies were unpopular across a diverse range of stakeholders, including policy makers, health providers, consumers and food industries, with a belief persisting that education and information were the best ways to address the obesity epidemic. An assessment of ‘unhealthy food’ taxes in Denmark, Finland and the USA on sweet foods and soft drinks found no change in demand, but argued that tax revenues raised (US $1 billion a year in the USA) could potentially be applied to fund other health and nutrition interventions. Some experts agree that, in Australia, consumption of fruit and promotion of public health messages, without altering the inherent food and exercise environment in which people live. In the other approach, governments attempt to influence choice through regulation. This may be through taxation of ‘unhealthy’ foods; tax breaks on healthy foods and costs of exercise; regulation of the production and processing of foods, for example to reduce levels of unhealthy fats and sugars; as well as attending to such factors as urban design as described above. The concept of consumer choice assumes that consumers make rational decisions based on accurate information. Social, environmental and cultural conditions have radically altered over recent decades towards those that promote a positive energy balance and population weight gain, which impact on the range and accessibility of ‘choices’ available, and potentially causing behavioural deregulation. For example, in Australia, the number of fast-food outlets has mushroomed, along with an increase in both parents working, a reduction in cost of food, and an increase in meals eaten away from home, with these meals having more fat, sugars and salts than home-cooked meals.

WHO proposed that education alone, whilst important, is unlikely to be solely adequate. They recommended cross-sector strategies, such as governments bringing public health and consumer protection ministries together, as has been proposed by the European Union. Acknowledging the role of globalisation, they have proposed considering modifying the World Trade Organisation’s free trade policy to prevent marketing and ‘dumping of unhealthy foods’ deemed undesirable in developed countries into developing ones. Rather, the WHO proposed that globalisation be leveraged to find solutions to the growing problem, through sharing of knowledge, research and innovation. An example cited is genetically modifying the starch in rice from high amylpectin content to high amylose to reduce its glycaemic index, as has developed for barley. Sharing of such technology between industries could impact the health of the two billion people for whom rice is a staple. However, the change in texture may make the product unacceptable in some areas, and glycaemic index alone may not be the best measure of a food product’s nutritional profile. The GI of basmati (long-grain, high-amyllose) rice is 43 and that of carrots is 80. However, the GI of a typical 150 g serving of rice is 18, whereas that of an 80 g serving of raw carrots is 6. Focusing on quality of carbohydrates and ignoring quantity is likely to fail. On the other hand, banning trans-fats in food production in the North America and parts of Western Europe was successful in that it did not change the subjective taste or affordability of food and appears to have improved lipid profile in the USA and potentially reduced trans-fat-associated heart disease in Costa Rica.

Through a combination of restrictions on advertising and sales, controls on use in public spaces, and significantly through application of taxes, there has been significant progress on alcohol and tobacco overuse and abuse. Subsidies have not always had a health agenda but rather an economic or even political one. However, taxing foods to reduce obesity is not without its pitfalls. In 2011 Denmark introduced a tax on foods containing more than 23% saturated fat, based on a landmark seven countries study that causally linked heart disease to serum cholesterol levels, which were in turn attributed to saturated fat intake. A recent BMJ article summarised the growing scientific challenge to these findings, claiming that the original data were misinterpreted, that controlling for levels of carbohydrates did not occur, and that newer cohort studies showed no causal link between saturated fat and cardiovascular disease. The author proposed that saturated fat in fact was protective against cardiovascular disease and diabetes. The repeal of the Danish ‘fat tax’ less than a year after its introduction, however, was not for this reason but because of its unpopularity with Danes and pressure from the food industry. This result could have been anticipated from a 2010 study in 9 European countries and the United Kingdom, which found that food taxes and subsidies were unpopular across a diverse range of stakeholders, including policy makers, health providers, consumers and food industries, with a belief persisting that education and information were the best ways to address the obesity epidemic. An assessment of ‘unhealthy food’ taxes in Denmark, Finland and the USA on sweet foods and soft drinks found no change in demand, but argued that tax revenues raised (US $1 billion a year in the USA) could potentially be applied to fund other health and nutrition interventions. Some experts agree that, in Australia, consumption of fruit
and vegetables would be even lower without the Goods and Services tax exemption. A low food taxes would translate in the developing world, where the double burden of under-nutrition and over-nutrition coexist, is uncertain. Compulsory fortification of certain foods such as wheat, sugar and oil exists in several developing countries to fight micronutrient deficiencies, but these foods may be the ones whose macronutrient profiles increase the risk of obesity. In contrast to a systemic approach to obesity is the belief that responsibility lies with the individual, with efforts aimed towards influencing individual behaviour. The most common methods are via dissemination of educational messages, often via national guidelines summarised as ‘food pyramid’ diagrams, and food labelling. Little is known about the effectiveness of such policies. A public health campaign encouraging people away from dietary fat towards increased carbohydrates has not halted obesity in developed countries. A constantly-shifting evidence base and an unbridled media fat towards increased carbohydrates has not halted obesity in developed countries.96,123 A constantly-shifting evidence base and an unbridled media

Conclusions

Unharnessed capitalism and globalisation appear to have led to improvements in income and quality of life in some settings, but to a concurrent state of increasing obesity and its sequelae of heart disease and type 2 diabetes in developing countries. The nutritional transition needs to be navigated with care and delicacy; for example, both overweight and underweight mothers have offspring at risk of metabolic sequelae in settings of secure food access, with rapid post-natal catch-up growth appearing to worsen this susceptibility. An international commitment is required to address a situation that threatens to derail economic progress of developing countries and indigenous populations in developed countries. Close scrutiny of nutritional research is required to ensure that rigorously-tested conclusions inform public health policy, paired with governmental commitment to placing health above profits. How can this be successful within a capitalism paradigm, with the foundational belief that in a free market people act in their own best interests, is unresolved, and an understanding of how to best achieve human metabolic health is still debated. Democracy and a free-market economy are currently viewed as the political ideals that nations should work towards to maximise freedom and standards of living of their citizens. Reducing obesity by consuming less seems ill-fitted to a capitalist construct with a profit motive. In contrast, applying resources to reduce of communicable diseases by developing urban infrastructure, sanitation, medications, housing and clean water are better suited towards a consumption paradigm. This is the dilemma of the obesity epidemic in a modernising, globalising world. Metabolic outcomes are influenced by a complex interplay of human evolution, genetics, ancient and current environmental influences, technological advancement and an evolving understanding of human nutrition. Perhaps the obesity pandemic is an opportunity to examine certain assumptions about capitalism and globalisation and consider a modified post-capitalist paradigm of human health and welfare.

References


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The Annals will appear twice a year and will consider for publication, papers on a wide range of topics relating to tropical and travel medicine. All papers will be refereed prior to acceptance for publication. Papers will be included in one of the following categories:

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b) Research Articles (up to 5,000 words)
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d) Research Reports (1,000-2,000 words)
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Figures to be included: 1/4 page size = 250 words; 1/2 page size = 500 words etc. One page with images is approximately 900 words, two pages with image is approximately 1,800 words. Manuscripts should be double spaced and a short summary should be included at the beginning of the paper after the title and author details. Title page with contributor names and addresses should be on a separate page. Each table and figure should be on a separate page together with an appropriate caption, explanatory notes etc. Any acknowledgements should be included at the end of the paper before the references. Where appropriate, authors must confirm in the paper that experimental procedures on humans and animals conformed to accepted international ethical guidelines. References should be numbered consecutively in order of first appearance in the text. For details of references, consult the “Uniform requirements for manuscripts submitted to biomedical journals” available at http://www.icmje.org/index.html.

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