

# Clinical Review

Clinical Review identifies issues in the medical literature of interest to clinicians in Africa. Essential references are given at the end of each section

## Medicine Review

### The aftermath of Ebola

The catastrophic epidemic of Ebola Virus infection in West Africa in 2014 has been well documented, and is likely to become part of medical history similar to past outbreaks of cholera or bubonic plague.

Much has been learnt about this serious infection since the outbreak. One example is the fact that the infection may relapse after initial recovery. A well-documented case concerns a British nurse who volunteered to help in the West African outbreak, and developed Ebola shortly after return to the UK. She recovered, but nine months later was readmitted to hospital with a similar illness, in which Ebola Virus was found in her cerebrospinal fluid (CSF).<sup>1</sup> She again recovered, though was left with mild neurological deficit. The authors commented that 'this finding fundamentally redefines what is known about the natural history of Ebola Virus infection'.<sup>1</sup>

Perhaps of relevance to this report is a study from Guinea of 802 patients who had recovered from proven Ebola infection.<sup>2</sup> At a median 350 days after viral clearance from their blood, 78% complained of persisting symptoms including malaise, myalgia, headache, abdominal pain, and visual disturbance. In some of the male patients studied, a positive PCR (polymerase chain reaction) was present in their semen. This worrying report appears to describe a 'post-Ebola syndrome', and raises the question of whether it may be related to chronic viral carriage.

Concerns have also been raised as to the way the Ebola epidemic was responded to. The response was slow and did not fully comply with the World Health Organization (WHO) guidelines on the management of such outbreaks. There also appears to have been poor co-ordination between local and external aid initiatives. Many of these problems are understandable, given the unprecedented nature of the epidemic. A recent article in the *British Medical Journal* reviews these problems and puts forward suggestions for improved responses to future similar outbreaks of serious infectious diseases.<sup>3</sup>

On a more optimistic note, the Ebola crisis stimulated the development of potential vaccines against the virus, and two recent *Lancet* papers report randomised trials from Guinea and Sierra Leone, with encouraging results.<sup>4,5</sup>

In 1859, the London physician Dr. John Snow made observations during a cholera epidemic which demonstrated the water-borne transmission of cholera. His

work led to effective sewage disposal and clean water supply; leading to the elimination of cholera from Britain. Let us hope that research from the 2014 West African Ebola outbreak will prevent such a dreadful disaster occurring again.

### Osteoporosis update

Osteoporosis is a neglected problem in Africa, and the extent of this disease is generally unknown. However, as life expectancy extends, it is likely to be on the increase, and the disease carries a heavy morbidity with its high risk of fractures.

Interestingly, osteoporosis was well recognised in Johannesburg, South Africa, as far back as the 1950s, where it was seen frequently in male urban migrant workers—often employed in the gold mines. Elegant studies in 1967 showed that it was associated with iron overload (due to drinking traditional beer, brewed in iron pots) and vitamin C deficiency.<sup>6</sup> Of a group of 110 men studied, 17 (15%) had advanced osteoporosis with vertebral body collapse on lateral spinal X-rays. When I worked at Baragwanath Hospital (Soweto) in 1982, the condition was still occasionally seen, though traditional beer brewing was less common and diets had improved. I remember well a comment made by the celebrated Johannesburg physician Harry Seftel, who said 'in the city of gold, the men of steel, have bones of clay'.<sup>6</sup>

Nowadays, osteoporosis is best diagnosed much earlier than the stage of bone fractures, and the ideal system is bone densitometry (not widely available in many parts of Africa). This measures bone mineral density (BMD) quantitatively, and there are agreed levels of intervention.<sup>7</sup>

In terms of treatment, lifestyle adjustment can be helpful—smoking and sedentary lifestyle are risk factors. Drugs such as corticosteroids strongly increase risk, and if possible steroids should be reduced or stopped. Other possible risk factors are alcohol excess, rheumatoid arthritis, low body weight (BMI <19.0) and family history. Caucasian races seem especially at risk and there is some evidence that osteoporosis frequency is less in the tropics than in more northerly or southerly countries.

Deficiencies of calcium and/or vitamin D should be corrected, but whether long-term supplementation helps is controversial. The main drug treatment is with bisphosphonates—there are many available, but weekly oral alendroate is the commonest used. These drugs reduce osteoclastic activity, thus reducing bone resorption. They are effective treatments, but are prone to gastrointestinal side-effects, and rarely can cause osteonecrosis of the jaw. It was previously thought that patients initiated on bisphosphonates should be treated for life, but this is now regarded as rarely necessary and the need for continuing treatment should be reassessed after five years of oral bisphosphonate treatment.

There are various less frequently used drugs including intermittent intravenous bisphosphonate, strontium ranelate, recombinant parathyroid hormone (PTH), denosumab (a new antiresorptive agent), and raloxifene (an oestrogen receptor modulator).

Diagnostic vigilance is needed to detect osteoporosis, particularly in older populations and those with known risk factors. The disease is likely to be seen more frequently in future African medical practice.

### Malaria news

Over the last 10 to 15 years there has been a significant decline in malaria transmission and incidence in Africa. Insecticidal bednets and artemisinin-based combination therapy have played an important role, as well as other strategies such as vector control and rapid diagnostics. It is agreed, however, that a multi-strategy approach is needed; so a recent report of a novel method of mosquito control is of interest.<sup>8</sup>

The project was a Kenyan-Dutch-Swiss initiative, and used the fact that mosquitoes are often attracted to human hosts by smell. The 'SolarMal' system is solar powered, and emits an odour which mimics the smell of humans using a blend of five organic chemicals which attract mosquitoes, and then traps them.

The study took place on Rusinga Island, Lake Victoria, Kenya; and different areas or 'clusters' were used for either intervention with the solar trap, or no intervention. The traps were used between dusk and dawn, and other preventative systems such as bednets continued as usual. Malaria was diagnosed by fever, as well as positive rapid diagnostic test.

Comparing areas using the mosquito traps to those that did not, there was a 30% reduction in malaria cases - 1552/6550 people (24%) versus 2002/5795 (35%). These are encouraging preliminary results, and it seems likely that the use of this clever system will spread.

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## Paediatrics Review

### Soil-transmitted helminths and physical and cognitive health of infected children

Infection with soil-transmitted helminths (STH) by the roundworms *Ascaris lumbricoides*, hookworms (*Ancylostoma duodenale* and *Necator americanus*), and the whipworm *Trichuris trichiura* is the most common parasitic human disease worldwide.<sup>1</sup> Chronic infections with these STH are considered to impair physical and cognitive development in school-aged children.<sup>2</sup>

Hookworm larvae develop in warm moist soil and

their life expectancy is short. Heavy infections cause iron-deficiency anaemia, particularly if the child's iron intake is low or loss is high; there may also be some protein loss from the gut.<sup>3</sup> Peak worm burden is in adults where up to 80% of the total population may be infected in this age group.<sup>4</sup>

The infective stages of *Ascaris lumbricoides* may persist in the soil for months. Most infections are small and asymptomatic. The major complication is intestinal obstruction which, though uncommon, is life threatening where prompt surgical services are unavailable. In vulnerable young children large, recurrent infections may impair gut absorption and increase the risk of malnutrition.

Although the majority of the worm burden of *Ascaris* and *Trichuris* is in children up to 30% may be in those older than 15 years-of-age.

*Trichuris trichiura* attaches to the mucosa of the caecum which is usually asymptomatic. However, heavy infections may extend as far as the rectum and cause severe symptoms of colitis associated with chronic loss of blood and failure to thrive. Existing drugs for community treatment, e.g. albendazole and mebendazole, have very low efficacy for treatment (8.4%) and for egg reduction (52%).<sup>5</sup> Albendazole + oxfantel pamoate is one of the best combination and has 68.6% cure rate and 99.2% egg reduction.<sup>5</sup>

The current World Health Organization (WHO) programmes for the control of STH target school-aged children (5–15 years-of-age) and also advises anthelmintics for pre-school-aged children (2–4 years-of-age), women of childbearing age and people in at-risk occupations, e.g. tea pickers.<sup>6</sup> The present goal is the treatment of 75% of children at risk by 2020. However, there is a good reason for deworming campaigns to be expanded to all age groups and particularly for hookworm as adults are the majority reservoir for this infection.<sup>1</sup>

A systematic review and meta-analysis was undertaken reporting STH prevalence before and after distribution of albendazole or mebendazole either targeted to children or delivered to the whole community.<sup>1</sup> Studies where follow up was less than three months or greater than 18 months after drug delivery were excluded. Of 56 studies eligible for the systematic review, 38 were included in the meta-analysis. Mass deworming led to a significantly greater reduction in prevalence of STH in children for hookworm (OR 4.6, 95% CI 1.8–11.6;  $p=0.002$ ) and for *Ascaris* (OR 116.4, 95% CI 2.1–125.8;  $p=0.009$ ) but there was no effect for *Trichuris*. This is not surprising as albendazole and mebendazole alone now have very poor efficacy for *Trichuris*.<sup>5</sup> The results support expanding deworming programmes community-wide and suggest that the WHO global guidelines for STH control should be re-evaluated.

Community-wide programmes for control of STH are highly cost-effective, particularly for hookworm, which adults act as a substantial reservoir.<sup>1,7</sup> Treatment every six months is also highly effective.<sup>7</sup> However, an alternative drug regimen is necessary to control *Trichuris*.<sup>5</sup> WASH (water, sanitation and hygiene) also play an important role but is both expensive, long-term and complex to undertake in underdeveloped societies and should be used alongside deworming campaigns.<sup>1</sup>

The most at-risk children are those living in rural communities with poor sanitation and lack of clean water (and thus hygiene), particularly children who do not go to school regularly, or at all, and thus miss out on school-based drug administration.

A common statement in textbooks, medical journals and even in social media is the importance of STH in the cause of poor growth and cognitive development in low- and middle-income countries. Although there is little disagreement that in individual cases hookworm and *Trichuris* can cause severe anaemia and Ascaris, intestinal obstruction, the above assumption has been recently challenged.<sup>8</sup> As society develops in wealth and education, especially in urban areas, many parents may have the incentive, and be able to afford to give their children regular anthelmintics.

A *Cochrane* systematic review was undertaken of randomised controlled trials (RCTs) and quasi-RCTs comparing anthelmintic drugs with placebo or no treatment in children  $\leq 6$ yr and reporting on weight, haemoglobin and formal tests of intellectual development, including school attendance, school performance and mortality.<sup>8</sup> Forty-five (45) trials were included, one trial evaluated mortality (over one million children) and 44 trials comprised 67 672 participants. Eight trials were in children known to be infected and 37 were in endemic areas. Treating children known to be infected, with a single dose of anthelmintic drug, may increase weight gain (by 0.2 to 1.3 kg) over the next one to six-month period (five trials, low quality evidence), but there was insufficient evidence regarding effects on haemoglobin (two trials), school attendance (zero trials), cognitive function (two trials), or physical well-being (three trials).

Community deworming programmes treating all children living in endemic areas with a dose of an anthelmintic probably has little or no effect on average weight gain (seven trials), even in settings with high prevalence of infection (two trials). A single dose, also probably has no effect on average haemoglobin (three trials), or average cognition (two trials). Regularly treating all children in endemic areas with anthelmintic drugs, given every three to six months may have little or no effect on average weight gain (10 trials). There is also reasonable evidence that regular treatment has no effect on average height (seven trials), average haemoglobin (seven trials), formal tests of cognition (five trials) or mortality (three trials).

Treating children known to have STH infection may have some nutritional benefits for the individual but mass treatment in endemic areas does not improve average nutritional status, haemoglobin, cognition, school performance, or survival.<sup>8</sup>

This *Cochrane* review stimulated a vigorous debate particularly regarding whether RCTs are an appropriate method to measure nutritional and educational benefits of preventive anthelmintic chemotherapy.<sup>9</sup> WHO issued a consensus statement to justify the present policy of

preventive chemotherapy, 'WHO's Strategic and Technical Advisory Group for Neglected Tropical Diseases (STAG-NTD), having appraised the *Cochrane Review* on STH infections together with the existing body of evidence (some of which was not taken into account in the *Cochrane Review*), notes that research has shown the benefits of deworming children with STH. STAG-NTD therefore continues to endorse WHO recommendations for mass deworming in areas where the prevalence of STH infection is over 20%. The administration of albendazole or mebendazole in such areas is safe and the most cost-effective strategy to reach infected children and improve their health and well-being'.<sup>10</sup>

STH have been around for some time and so have available methods to control them (but not necessarily the most effective drugs, especially for *Trichuris*) yet it still seems that we are not clear on how best to undertake control, nor, in fact, how serious a problem STH are in a changing world. It is important to keep an open mind regarding the optimal way to reduce the worm burden in the community and the most effective instruments to measure the effect of mass treatment on the development and health of children.<sup>11</sup>

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