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# VACCINES FOR TYPHOID FEVER

Typhoid is a potentially fatal infection caused by a bacteria known as *Salmonella typhi*. It may also be caused by *Salmonella paratyphi*.In 2004, it was estimated that there were 21million cases of typhoid fever and 216,000 - 600,000 deaths worldwide from the disease annually.[1]Although the disease is endemic in Asia, the Middle East, Africa, and South and Central America, the highest burden is in Asia. School age children and adults are mainly affected. However in some areas, incidence rates among preschool children (below 5 years) are similar to those of school age children. Symptoms of the disease can be mild or severe and include fever, headache, constipation or diarrhoea, abdominal pain, loss of appetite, enlarged liver or spleen, and rose-coloured spots on the chest. In severe cases, the mental state could be altered leading to confusion, psychosis and other symptoms attributable to cerebral dysfunction, delirium and shock.[1,2,3,4]

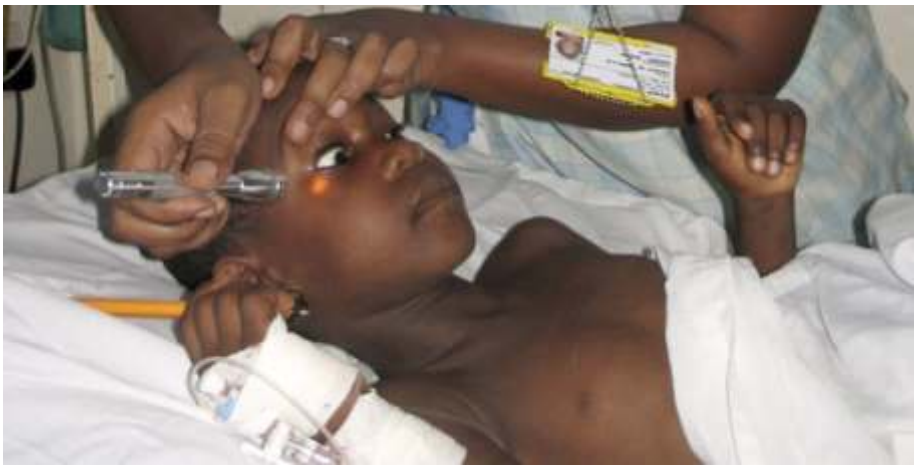
The disease is spread through the ingestion of food or drink contaminated by the faeces or urine of infected people. As such, it thrives where water sanitation and hygiene are poor or inadequate. Control of the disease, therefore, is mainly through improved sanitation and food hygiene. Drugs such as ampicillin, chloramphenicol, co-trimoxazole and amoxicillin have been used to treat typhoid fever but recent emergence of multidrug resistant strains has created a problem in the use of these drugs for the treatment of typhoid.[1]This has led to the use of quinolone derivatives such as ciprofloxacin, ofloxacin and third generation cephalosporins such as ceftriaxone and cefixime.

Due to the lack of economic means for improved sanitation and food hygiene in many endemic countries and the development of drug resistant strains, vaccines may prove to be the most viable means of controlling the disease. The World Health Organization has recommended the programmatic use of typhoid vaccines for controlling the disease in countries where the disease is endemic.[1]

Currently, typhoid vaccines are mainly used by travellers to endemic areas. Two typhoid vaccines have been licensed for use internationally. These are the live, oral Ty21a vaccine and the injectable Vi Polysaccharide vaccine for people above 2yrs. A third vaccine, *Vi-rEPA vaccine, has not yet been licensed, but has been evaluated in a randomized controlled trial in children below two years of age.*

A Cochrane Systematic review[5] of existing research sought to assess whether these vaccines were effective in preventing the disease. Eighteen randomized controlled trials (RCTs) were included in the review. Of these, 12 RCTs evaluated the efficacy of these vaccines. The results of the review show that both Ty21a and Vi Polysaccharide vaccines are efficacious. The Vi-rEPA vaccine, though not yet licensed, is also efficacious and may confer longer immunity than the other two vaccines.

The review showed that a three-dose schedule of Ty21a vaccine can prevent one-third to one-half cases of typhoid in the first two years after vaccination. A single dose of the Vi Polysaccharide vaccine can prevent about two-thirds of typhoid fever cases in the first year after vaccination and between 45-69% of cases in the second year. Two doses



of the Vi-rEPA vaccine are able to prevent 50-96% of typhoid cases in the first two years after vaccination.

For all tested vaccines, adverse events such as nausea, vomiting fever and swelling at injection site were not significantly increased in people who took the vaccine.

The World health Organization recommends routine immunization of populations where typhoid fever is endemic[1] and where improved sanitation is needed to control the disease; this has been poor due to slow socioeconomic progress.


**References**

1. World Health Organisation. Typhoid vaccine: WHO position paper. *Weekly Epidemiological Record* 2008;**83**(6):49-60.

2. World Health Organization. Health Topics – Typhoid fever. http://www.who.int/topics/typhoid_fever/en/

3. http://www.who.int/immunization/topics/typhoid/en/index.html

4. http://www.who.int/water_sanitation_health/diseases/typhoid/en/

5. Anwar E, Goldberg E, Fraser A, Acosta CJ, Paul M, Leibovici L. Vaccines for preventing typhoid fever. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD001261. DOI: 10.1002/14651858.CD001261.pub3.


# EVIDENCE AT YOUR FINGERTIPS

(From the Cochrane Library)

## TECHNICAL SUMMARY

### Dihydroartemisinin-piperaquine for treating uncomplicated *Plasmodium falciparum* malaria

#### Background

Malaria is an infectious disease caused by the plasmodium parasite.

There are five species of plasmodium. One of the species, *plasmodium falciparum*, is responsible for over 90% of malaria cases. It is spread by the female anopheline mosquito. The disease is characterized by fever which may be accompanied by other symptoms such as headaches, rigors, tiredness, abdominal pains and vomiting.

The World Health Organization (WHO) recommends the use of artemisinin-based combination therapies (ACTs) for the treatment of *P.falciparum* malaria. Five ACTs are recommended by the WHO, namely: dihydroartemisinin-piperaquine (DHA-P); artesunate plus mefloquine (AS+MQ); artemether-lumefantrine – six-dose regimen (AL6); artesunate plus amodiaquine (AS+AQ); and artesunate plus sulfadoxine-pyrimethamine (AS+SP).

# Evidence At Your Fingertips *(continued)*

Dihydroartemisinin-piperaquine (DHA-P) comprises of dihydroartemisinin and piperaquine (DHA-P). Dihydroartemisinin is the active metabolite of the artemisinin derivatives. It relieves clinical symptoms and clears malaria parasites from the blood faster than other antimalarial drugs. Piperaquine is a bisquinoline antimalarial whose mode of action is thought to be similar to that of chloroquine.

Generally, artemisinin and its derivatives have been reported to be safe and well tolerated. However, a few small studies have shown an association between DHA-P and prolongation of QT interval, which is a cardiac conduction defect that can lead to fatal arrhythmias.

Review Objective: To evaluate the effectiveness and safety of DHA-P compared to other ACTs for treating uncomplicated *P. falciparum* malaria in adults and children.

Main Results:

- Twenty seven randomized controlled trials involving a total of 16,382 participants were included in the review. Some trials had multiple arms.
- Participants were adults and children with symptomatic, microscopically confirmed uncomplicated *P.falciparum* (including those with *P. vivax* co-infection). Pregnant and lactating mothers were excluded.
- Intervention were a three-day course of DHA-P compared to a three-day course of a WHO recommended ACT.
- *DHA-P versus Artemether-lumefantrine: Fifteen trials assessed this comparison – Africa (11), Asia (3), Oceania (1).*

*Total Failure*

*PCR unadjusted failure treatment failure was lower with DHA-P at day 28 in Africa.* (RR 0.34, 95% CI 0.30 to 0.39, nine trials, 6200 participants, *high quality evidence). When PCR adjusted, the treatment failure, was less than 5% for both DHA-P and AL6 but consistently lower for DHA-P* (RR 0.42, 95% CI 0.29 to 0.62, nine trials, 5417 participants, *high quality evidence).* The post-treatment prophylactic effect of DHA-P appears to be longer than AL6 (PCR unadjusted treatment failure at day 63: RR 0.71, 95% CI 0.65 to 0.78, two trials, 3200 participants, *high quality evidence*). In Asia and Oceania, there was no difference at day 28 (four trials, 1143 participants, *moderate quality evidence*), or day 63 (one trial, 323 participants, *low quality evidence*) in treatment failure rates before and after PCR adjustment.

*Adverse Events*

Although, DHA-P was associated with higher frequency of drug-related vomiting and pruritus, overall, there was no difference in these types of serious adverse events between DHA-P and AL6. There was no difference in prolonged QTc (*low quality evidence*), and no cardiac arrhythmias were reported. The frequency of other adverse events is probably similar with both

combinations (*moderate quality evidence*).

- ***DHA-P versus artesunate plus mefloquine:*** Eleven trials assessed this comparison – Asia(10) and South America (1)

*Total Failure*

In Asia, there was no difference in PCR-unadjusted treatment failure between comparison groups at day 28 (eight trials, 3487 participants).When PCR-adjusted, the treatment failure at day 28 was less than 5% for both ACTs (eight trials, 3482 participants) but lower for DHA-P in two trials. (PCR-adjusted treatment failure: RR 0.41 95% CI 0.21 to 0.80, eight trials, 3482 participants, *high quality evidence*). None of the combinations showed a consistent benefit in preventing new infections over 63 days follow-up period (PCR-unadjusted treatment failure: five trials, 2715 participants, *moderate quality evidence*).

In South America, although recrudescences and new infections were very rare with either DHA-P or AS+MQ over a 63 day follow-up period, new infections were lower with AS+MQ (RR 6.19, 95% CI 1.40 to 27.35, one trial, 445 participants). When PCR adjusted, however, there were no differences observed. (PCR-adjusted treatment failure: one trial, 435 participants, *low quality evidence*).

*Adverse Events*

DHA-P is associated with less nausea, vomiting, dizziness, sleeplessness, and palpitations than artesunate plus mefloquine (*moderate quality evidence*). However, DHA-P is associated with more frequent prolongation of the QTc interval (*low quality evidence*). No cardiac arrhythmias were reported.

- *DHA-P versus artesunate plus amodiaquine:* Four trials assessed this comparison - two in Africa and two in Asia.

Total failure

In both Africa and Asia, PCR-unadjusted treatment failure at day 28 was lower following treatment with DHA-P(RR 0.49, 95% CI 0.41 to 0.59, two trials, 2800 participants, Africa) (RR 0.38 95% CI 0.18 to 0.77, two trials, 482 participants, Asia). After PCR-adjustment however, the difference between treatments was no longer statistically significant in the African trials but remained lower with DHA-P in the Asian trials.

Adverse events

The frequency of serious adverse events was lower with DHA-P, and despite few events, this reached statistical significance (RR 0.40 95% CI 0.19 to 0.87, two trials, 2805 participants)

Pyrexia was statistically more common with DHA-P (RR 1.18 95% CI 1.02 to 1.37, one trial, 2471 participants.

- *DHA-P versus artesunate plus sulfadoxine-pyrimethamine:*One trial conducted in Oceania assessed this comparison.

Total failure

PCR-adjusted treatment failure at day 28 was greater than 10% in both arms but there were no statistically significant differences in treatment failure between the two arms (one trial, 223 participants)

*Adverse events*

There was no difference in adverse events between the groups

Conclusion: In Africa, DHA-P is an effective alternative to AL. It reduces treatment failure compared to AL, has a simple dosing regimen and longer prophylactic effect following treatment. DHA-P is as effective as AS+MQ which is widely used in Asia. It is however better tolerated than AS+MQ.

*Zani B, Gathu M, Donegan S, Olliaro PL, Sinclair D. Dihydroartemisinin-piperaquine for treating uncomplicated Plasmodium falciparum malaria. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD010927. DOI: 10.1002/14651858.CD010927.*

# PLAIN LANGUAGE SUMMARIES

## Administration of antimalarial drugs to whole populations

Malaria is the most important mosquito-borne disease caused by a parasite, accounting for an estimated 660,000 deaths annually. Fortunately, malaria is both preventable and treatable. Several malaria control tools currently exist, and new and innovative approaches are continually under development.

The administration of drugs against malaria to whole populations, termed mass drug administration (MDA), was a component of many malaria elimination programmes in the 1950s, and is once again attracting interest as a malaria elimination tool. As a consequence, it is important to review the currently available literature in order to assess the potential for this strategy to reduce malaria burden and transmission, and to identify gaps in our understanding.

This review assessed the impact of MDA on several malaria-specific outcome measures. Thirty-two studies were included in this review, from sites in Asia, Africa, Europe and the Americas.

The review found that although MDA can reduce the initial risk of malaria-specific outcomes, these reductions are often not sustained. However, a few studies conducted on small islands or in highland areas did show sustained impact more than six months after MDA.

Adverse events were inadequately addressed in most studies. Notable severe drug reactions, including haemolysis, haemoglobinuria, severe anaemia and death, were reported with 8-aminoquinoline plus schizonticide drug co-administration, while severe skin reactions were reported with sulphadoxine-pyrimethamine plus artesunate plus primaquine.

Assessing the true impact of MDA programmes can be a challenge due to the heterogeneity of the study methods employed. Nonetheless, this review can help guide future antimalarial MDA interventions and their evaluation.

*Poirot E, Skarbinski J, Sinclair D, Kachur SP, Slutsker L, Hwang J. Mass drug administration for malaria. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD008846. DOI: 10.1002/14651858.CD008846.pub2.*

## Exercise programs for people with dementia

### Background

In future, as the population ages, the number of people in our communities suffering with dementia will rise dramatically. This will not only affect the quality of life of people with dementia but also increase the burden on family caregivers, community care, and residential care services. Exercise is one lifestyle factor identified as a potential means of reducing or delaying progression of the symptoms of dementia.

### Study Characteristics

This review evaluated the results of 16 trials (search date August 2012), including 937 participants, that tested whether exercise programs could improve cognition, activities of daily living, behaviour, depression, and mortality in older people with dementia or benefit their family caregivers.

### Key Findings

There was promising evidence that exercise programs can significantly improve the cognitive functioning of people with dementia and their ability to perform daily activities, but there was a lot of variation between trial results that we were not able to explain. The studies showed no significant effect of exercise on mood. There was little or no evidence regarding the other outcomes listed above. Further well-designed research is required to examine these outcomes and to determine the best type of exercise program for people with different types and severity of dementia.

Quality of Evidence

Twelve additional trials were included in this updated review compared with the four included in the previous version of the review. As a result the number of participants increased to 937 at baseline and 798 (85.2%) completed the trials, compared with 280 at baseline and 208 (74%) completing the trials in our previous review. These are encouraging results. The number and quality of included trials were sufficient to address the first three objectives relating to the effect of exercise on cognition, ADLs, and depression. However, only one trial was included in the analyses of the effect of exercise on challenging behaviours and caregiver burden, and no analyses were completed for the following outcomes: mortality in people with dementia, caregiver quality of life, caregiver mortality, and use of healthcare services.

The authors have no conflicts of interest.

Forbes D, Thiessen EJ, Blake CM, Forbes SC, Forbes S. Exercise programs for people with dementia. Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD006489. DOI: 10.1002/14651858.CD006489.pub3.

# New and Updated Reviews from the Cochrane Library

The following reviews recently published in the Cochrane Library were authored or co-authored by Nigerians.

New Reviews

- Prophylactic versus selective blood transfusion for sickle cell disease in pregnancy by *Babasola O Okusanya, Olufemi T Oladapo*. Issue 12, 2013.

Updated Reviews

- Interventions for Mooren's ulcer by *Mahmoud B Alhassan, Mansur Rabiu and Idris O Agbabiaka*. Issue 1, 2014
- Routine vitamin A supplementation for the prevention of blindness due to measles infection in children by *Segun Bello, Martin M Meremikwu , Regina I Ejemot-Nwadiaro, Olabisi Oduwole*. Issue 1, 2014

Other Recent Reviews

- Interventions for the prevention of mycobacterium avium complex in adults and children with HIV by *Muhammed Mubashir B Uthman, Olalekan A Uthman and Ismail Yahaya. Issue 4, 2013.*
- Surgical versus non-surgical management of abdominal injury by *Angela Oyo-Ita, Udey G Ugare, Ikpeme A Ikpeme. Issue 11, 2012.*
- Home or community-based programmes for treating Malaria by *Charles I Okwundu, Sukrti Nagpal, Alfred Musekiwa, David Sinclair. Issue 5, 2013.*
- Interventions for HIV-associated nephropathy by *Ismail Yahaya, Olalekan A Uthman, Muhammed Mubashir B Uthman. Issue 1, 2013.*
- Intramuscular versus intravenous anti-D for preventing Rhesus alloimmunization during pregnancy by *Charles I Okwundu, Bosede B Afolabi. Issue 1, 2013*.

# ANNOUNCEMENTS

- Issue 1, 2014 is online – The complete issue of Issue 1, 2014 is now online. Please visit www.thecochranelibrary.com

- Cochrane Colloquium 2014: The 22nd Annual Cochrane Colloquium will be hosted by the South Asian Cochrane Network and Centre and will take place at the Hyderabad International Convention Centre, Hyderabad, India, 21-26 September 2014.

**KEY DATES FOR COLLOQUIUM**

- Call for abstracts and workshops: 3 February
- Early registration opens: 3 March
- Call for stipend applications: 3 March
- Deadline for abstract and workshop submissions: 24 March
- Meeting requests open: 12 May
- Abstracts and workshops notification: 12 May
- Receipt of stipends application deadline: 19 May
- Stipends applicants notified: 23 June
- Early registration closes: 14 July
- Regular registration begins: 15 July
- Meeting request deadline: 4 August

- Cochrane Colloquium 2016 in Korea: The 2016 Cochrane Colloquium will be hosted by the Korean Branch of the Australasian Cochrane Centre
- How can we serve you better - Please feel free to contact us and let us know how we can tailor the *Info Sheet* to better meet your needs. Send your emails to cochranenigeria@yahoo.co.uk

- Cochrane Game Changers
The Cochrane Collaboration is inviting bids from people with large-scale innovative ideas that can transform the way evidence research is produced, accessed, used and communicated. Entries should be submitted by 31st March 2014. For full details visit: http://www.cochrane.org/features/cochrane-opens-stage-innovators-game-changer-ideas

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*Please visit our website*: nigeria.cochrane.org
*Email us at*: cochranenigeria@yahoo.co.uk

*Follow us on*:

*Nigerian Branch of the South African Cochrane Centre*

*@cochranenigeria*

*Call us on*:
Moriam:+234 (0)8039733998
Bisi:+234 (0) 8056071976
Emmanuel: +234 (0) 8037236919

*Address:*
Nigerian Branch of the South African Cochrane Centre
Calabar Institute of Tropical Diseases Research and Prevention
University of Calabar Teaching Hospital,
Moore Road
GPO Box 3134, Calabar
Cross River State

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