PHC Chapter 10: Infections and related conditions

10.1 ANTISEPTICS AND DISINFECTANTS

DESCRIPTION

Disinfectants are used to kill micro-organisms on working surfaces and instruments, but cannot be relied on to destroy all micro-organisms.

Antiseptics are used for reducing bacterial load on skin and mucous membranes.

Disinfecting surfaces

Guidelines for the use of disinfectants

» Cleansing (removal of visible soiling) is the first and most important step in chemical disinfection.
» The disinfectant fluid must entirely cover the object and penetrate all crevices.
» Use the recommended strengths for specific purposes.
» Disinfectants cannot sterilise surgical instruments.
» No chemical agent acts immediately; note the recommended exposure time.
» Equipment must be rinsed with sterile water after immersion in a chemical disinfectant e.g. chlorhexidine solution, 0.5% in 70% alcohol.
» Avoid recontamination at this stage.
» Make sure that the rinsing water and all other apparatus are sterile.
» Equipment must not be stored in chemical disinfectants.
» The best disinfectant for killing HIV and other pathogens is a chlorinated solution such as bleach or hypochlorite:
  - Solutions must be freshly prepared.
  - Discard after 24 hours to disinfect properly.
  - Do not use on the skin.

Intact skin

» Use alcohol swabs to clean skin surface before injections are administered.
» Use antiseptics like povidone iodine or chlorhexidine for surgical scrubbing.

Wounds and mucous membranes

- Use chlorhexidine 0.05% aqueous solution to clean dirty wounds.
- Use sodium chloride 0.9% and sterile water on clean wounds.

Disinfectant	Indications	Directions for application
• Chlorhexidine solution: 0.05% aqueous solution.	» Cleaning dirty wounds.	» Remove all dirt, pus and blood before use.
• Chlorhexidine solution: 0.5% in 70% alcohol.	» Skin disinfection before surgery.	» Apply as a preoperative skin prep agent to the relevant area.
• Povidone iodine: o solution 10%. o ointment 10%. o cream 5%.	» Skin and wound infections **Contraindication**: iodine allergy.	» Use ointment for skin infection. » Use solution for cleaning skin and wounds. » **Avoid** using on large wounds because of danger of iodine absorption.

Table 10.1: Disinfectants

Articles and instruments
Adhere to the appropriate cleansing and disinfection policy.

10.2 CHICKENPOX

B01.9/B01.8

DESCRIPTION

A mild viral infection that presents 2–3 weeks after exposure, with:
» mild fever preceding the rash
» lesions beginning on the trunk and face, later spreading to the arms and legs
» small, red, itchy spots that turn into blisters and crusts. These stages may all be present at the same time.

Chickenpox is infective from the start of the fever until 6 days after the lesions have appeared or until all the lesions have crusted.
The infection is self-limiting, with a duration of about 1 week.
Complications such as secondary bacterial infection, encephalitis, meningitis and pneumonia may occur (more common in adults and immunocompromised patients).

GENERAL MEASURES

» Isolate from immunocompromised people and pregnant women until all lesions have crusted.
» Ensure adequate hydration.
» Cut fingernails short and discourage scratching.

MEDICINE TREATMENT

CAUTION
Avoid the use of aspirin in children and adolescents < 16 years of age with acute febrile illness because of risk of Reye's syndrome.

For itch:
- Calamine lotion, applied as needed.

In severe cases

Children
- Chlorphenamine, oral, 0.1 mg/kg/dose 6–8 hourly. See dosing table, pg 23.3.

Adults
- Chlorphenamine, oral, 4 mg, 6–8 hourly.

For fever with distress:

Children
- Paracetamol, oral, 10–15 mg/kg/dose 6 hourly when required. See dosing table, pg 23.8.

Adults

- Paracetamol, oral, 1 g 4–6 hourly when required to a maximum of 4 doses per 24 hours.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4 g in 24 hours.

If skin infection is present due to scratching, treat as for bacterial skin infection. See Section 5.4: Bacterial infections of the skin.

Treatments with antiviral agents are recommended for:

» Immunocompromised patients.
» All patients with severe chickenpox (irrespective of duration of rash).
  - Extensive rash.
  - Haemorrhagic rash.
  - Visceral involvement.
  - Presence of complications.
» Adults and adolescents presenting within 48 hours of the onset of the rash.
» Pregnant women.

Children

- Aciclovir, oral, 20 mg/kg/dose 6 hourly for 7 days (Doctor prescribed).

Weight kg	**Dose** mg	**Use one of the following:**			**Age** months/years
		Susp	**Tablet**		
		200 mg /5 mL	200 mg	400 mg	
>3.5–5	100	2.5 mL	–	–	>1–3 months
>5–7	140	3.5 mL	–	–	>3–6 months
>7–9	160	4 mL	–	–	>6–12 months
>9–11	200	5 mL	1 tablet	½ tablet	>12–18 months
>11–14	240	6 mL	–	–	>18 months–3 years
>14–25	400	10 mL	2 tablets	1 tablet	>3–5 years
>25–35	600	15 mL	3 tablets	1½ tablet	>7–11 years
>35–55	700	–	3 ½ tablets	–	>11–15 years

Adults

- Antiviral, (active against varicella zoster) e.g.:
- Aciclovir, oral, 800 mg 6 hourly for 7 days (Doctor prescribed). *LoE:IIIb*[1]

REFERRAL

» Complications such as:
  - meningoencephalitis
  - pneumonia
» Severely ill patients.
» Pregnant women.
» Asymptomatic neonates whose mothers had developed chickenpox during the period from 7 days before to 7 days after delivery.
» Neonates with clinical chickenpox.

10.3 CHOLERA

See Chapter 2: Gastrointestinal conditions.

10.4 DYSENTERY, BACILLARY

See Chapter 2: Gastrointestinal conditions.

10.5 FEVER

R50.0-1/R50.8-9

DESCRIPTION

Fever, i.e. temperature ≥ 38°C, is a natural and sometimes useful response to infection, inflammation or infarction.

Fever alone is not a diagnosis.

Fever may be associated with convulsions in children < 6 years of age, but is not a cause of the convulsions.

Note:

» Temperature > 40°C needs urgent lowering in children.
» Fluid losses are increased with fever.
» Malaria must be considered in anyone with fever who lives in a malaria endemic area, or who has visited a malaria area in the past 12 weeks.

GENERAL MEASURES

Children

» Caregivers should offer the child fluids regularly to keep them well hydrated (where a baby or child is breastfed the most appropriate fluid is breast milk).
» Dress child appropriately for the weather.
» Ensure the child is rested.
» Following contact with a healthcare professional, parents and carers who are looking after their feverish child at home should seek further advice if:
  - the child has a convulsion
  - the child develops a non-blanching rash
  - the parent or carer feels that the child is less well than when they previously sought advice
  - the parent or carer is more concerned than when they previously sought advice
  - the fever lasts > 2 days

Note: Tepid sponging and evaporative cooling are not recommended, as this causes the child to shiver which actually increases the core temperature.

Adults

Maintain hydration.

MEDICINE TREATMENT

Consider treatment with paracetamol in adults with associated tachycardia, possibility of worsening cardiac conditions, and adults and children who are in distress.

Antipyretic agents are not indicated with the sole aim of reducing body temperature in children and adults with fever.

Children

- Paracetamol, oral, 10–15 mg/kg/dose 6 hourly when required. See dosing table, pg 23.8.

Adults

- Paracetamol, oral, 1 g 4–6 hourly when required to a maximum of 4 doses per 24 hours.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4 g in 24 hours.

CAUTION

Do not treat undiagnosed fever with antibiotics, except in children < 2 months of age who are classified as having

POSSIBLE SERIOUS BACTERIAL INFECTION.

Do not give aspirin to children and adolescents with acute febrile illness.

Children < 2 months of age, fulfilling any criterion of possible serious bacterial infection (see referral criteria):

- Ceftriaxone, IM, 80 mg/kg/dose immediately as a single dose. See dosing table, pg 23.3.
  - Do not inject more than 1 g at one injection site.

CAUTION: USE OF CEFTRIAXONE IN NEONATES AND CHILDREN

» If SUSPECTING SERIOUS BACTERIAL INFECTION in neonate, give ceftriaxone, even if jaundiced.

» Avoid giving calcium-containing IV fluids (e.g. Ringer Lactate) together with ceftriaxone:
- If ≤ 28 days old, avoid calcium-containing IV fluids for 48 hours after ceftriaxone administered.
- If > 28 days old, ceftriaxone and calcium-containing IV fluids may be given sequentially provided the giving set is flushed thoroughly with sodium chloride 0.9% before and after.
- Preferably administer IV fluids without calcium contents.

» Always include the dose and route of administration of ceftriaxone in the referral letter.

REFERRAL

» All children < 2 months of age with any one of the following criteria of possible serious bacterial infection:
- axillary temperature > 37.5°C
- bulging fontanelle
- decreased movement/moves only ,.when stimulated
- convulsions with current illness
- decreased level of consciousness
- breathing difficulties, i.e. respiratory rate > 60, nasal flaring, chest in-drawing or apnoea

  - pus forming conditions, i.e. umbilical redness extending to the skin or draining pus, many or severe skin pustules, pus draining from eye
» All children in whom a definite and easily managed cause is not found.
» Fever that lasts > 2 days without finding a treatable cause.
» Fever that recurs.
» Fever combined with:
  - signs of meningitis
  - toxic-looking patient
  - convulsion
  - coma or confusion
  - jaundice
  - failure to feed

10.6 GIARDIASIS

See Chapter 2: Gastrointestinal conditions.

10.7 MALARIA

Note: notifiable medical conditions.

Refer to the most recent Malaria Treatment Guidelines from the Department of Health for the most suitable management in the various endemic areas.

Global malaria endemic areas:
https://www.iamat.org/risks/malaria?gclid=CjwKEAiAjIbBBRCitNvJ1o257WESJADpoUt072u5_X4Wb0fVtkQLiEFrWye263Ef_on8eykkOwLK_hoCFtDw_wcB

Local endemic areas:

https://www.santhnet.co.za/index.php/travel-health-advice/travel-advice/malaria-advice-for-travellers/item/330-malaria-risk-map-for-south-africa-2017.html

DESCRIPTION

Malaria is an infection of red blood cells by a parasite micro-organism called Plasmodium. Five species of Plasmodium are known to cause malaria in humans in Africa. The five species are:

» *Plasmodium falciparum (P. falciparum)*
» *Plasmodium vivax (P. vivax)*
» *Plasmodium ovale (P. ovale)*
» *Plasmodium malariae (P. malariae)*
» *Plasmodium knowlesi (P. knowlesi)*

The parasites are usually transmitted to humans by the bite of a vector mosquito. In South Africa, *P. falciparum* is the most common and the most dangerous of the malaria species. Malaria caused by *P. falciparum* is an acute febrile illness that may progress rapidly to severe disease if not diagnosed early and treated adequately.

Symptoms and signs of malaria are non-specific.

The most important element in the diagnosis of malaria is a high index of suspicion in both endemic and non-endemic areas. Any person resident in or returning from a malaria area **and** who presents with fever (usually within 3 months of possible exposure to vector mosquito bites) should be tested for malaria. The progression of *P. falciparum* malaria to

severe disease is rapid, and early diagnosis and effective treatment is crucial. **Pregnant women, young children ≤ 5 years of age and people living with HIV/AIDS are at particularly high risk of developing severe malaria**.

Symptoms and signs of malaria may include:

- severe headache
- fever > 38°C
- muscle and joint pains
- diarrhoea
- shivering episodes
- nausea and vomiting
- flu-like symptoms
- dry cough

Severe disease may present with one or more of the following additional clinical features:

- prostration (severe general body weakness)
- sleepiness, unconsciousness or coma, convulsions
- respiratory distress and/or cyanosis
- jaundice
- renal failure
- shock
- repeated vomiting
- hypoglycaemia
- severe anaemia (Hb < 7 g/dL)
- haemoglobinuria/black urine
- abnormal bleeding

DIAGNOSIS

Microscopic examination of thick and thin blood smears. Thick films are more sensitive than thin films in the detection of malaria parasites.

Where rapid diagnostic tests, e.g. HRP2 antigen dipsticks are available, these can be used to diagnose malaria within 10–15 minutes.

Note:

- Rapid tests may remain positive up to 1 month after successful treatment
- One negative malaria test does not exclude the diagnosis of malaria. Request 2nd test.

GENERAL MEASURES

- Provide supportive and symptomatic relief.
- Monitor for complications.
- Ensure adequate hydration.
- Carefully observe all patients with P. falciparum malaria for the first 24 hours for features of severe malaria.

MEDICINE TREATMENT

All first doses of antimalarial medicines must be given under supervision and patients must be observed for at least an hour as vomiting is common in patients with malaria. Treatment must be repeated if the patient vomits within the first hour. Vomiting oral treatment is one of the commonest reasons for treatment failure.

In areas with high incidence of malaria (whether locally transmitted or imported) it should be definitively diagnosed and treated at PHC level. In other areas, patients should be referred for treatment.

10.7.1 MALARIA, NON-SEVERE/UNCOMPLICATED

B50.9/B51.9/B52.9/B53.0/B54

Note: notifiable medical condition.

MEDICINE TREATMENT

- Artemether/lumefantrine, oral, 20/120 mg, with fat-containing food/full cream milk to ensure adequate absorption.
  - Give the first dose immediately.
  - Follow with second dose 8 hours later.
  - Then 12 hourly for another 2 days (total number of doses in 3 days = 6).

Weight kg	Artemether/lumefantrine 20/120 mg/tablet	**Tablet(s)**	**Age** months/years
>5–15	20/120 mg	1 tablet	6 months–3 years
>15–25	40/240 mg	2 tablets	>3–8 years
>25–35	60/360 mg	3 tablets	>8–12 years
>35	80/ 480 mg	4 tablets	>12 years and adults

For fever in children < 5 years of age:

Children

- Paracetamol, oral, 10–15 mg/kg/dose 6 hourly when required. See dosing table, pg 23.8.

REFERRAL

Urgent

» All patients with any sign of severe (complicated) malaria, see Section 10.7.2: Malaria, severe/complicated.
» All patients presenting to PHC clinics in areas that do not stock antimalarials.
» Vomiting leading to inability to retain medication.
» Patients not responding to oral treatment within 48 hours.
» After 1st dose of artemether/lumefantrine 20/120 mg:
  - All children < 2 years of age.
  - Pregnant women.
  - Patients with co-morbidities such as HIV, diabetes etc.
  - Patients > 65 years of age.

10.7.2 MALARIA, SEVERE/COMPLICATED

B50.0/B50.8

Note: notifiable medical condition.

DESCRIPTION

Any one of the following is a sign of severe (complicated) malaria, is associated with a higher mortality, and requires urgent referral (after initial artesunate dose as below):

» prostration (severe general body weakness)
» sleepiness, confusion, unconsciousness or coma, convulsions
» respiratory distress and/or cyanosis
» jaundice
» renal failure
» shock
» repeated vomiting
» hypoglycaemia
» severe anaemia (Hb<7g/dL)
» haemoglobinuria/black urine
» abnormal bleeding

MEDICINE TREATMENT

Treatment may be commenced before referral in clinics designated by the regional malaria control programme provided they have facilities to diagnose malaria (either microscopy or rapid antigen point of care tests) and healthcare workers trained in the management of severe malaria.
Correct hypoglycaemia immediately, if present.

Adults and children ≥ 20 kg:

- Artesunate IM, 2.4 mg/kg immediately as a single dose and refer urgently.
  - If transfer to referral hospital is delayed, administer second dose at 12 hours and third dose at 24 hours.

LoE:Ia[2]

Children < 20 kg:

- Aresunate IM, 3 mg/kg immediately as a single dose and refer urgently.
  - If transfer to referral hospital is delayed, administer second dose at 12 hours and third dose at 24 hours.

LoE:IIIb[3]

Note: For all patients requiring referral, the patient must be transferred to reach the referral hospital **within 6 hours** of being seen at the PHC facility.
Advise referral hospital that an initial dose has been administered.

REFERRAL

Urgent
All patients.

For dosing of artesunate, see Figure 10.1: Dosing of artesunate, below.

GUIDELINES FOR ADMINISTRATION OF INJECTABLE ARTESUNATE FOR SEVERE MALARIA

WHO RECOMMENDED TREATMENT [2]

Artesunate powder 60mg | Bicarbonate ampoule | Saline solution *

PRODUCT DESCRIPTION [1]

Dose: For children < 20 kg: 3.0 mg/kg
For children > 20 kg and adults: 2.4 mg/kg

Can be given by intravenous route (IV) or intramuscular route (IM).
IV is the preferred route of administration.
Please refer to the patient information leaflet for more information.

* Water for injection is not an appropriate dilutant

1 WEIGH THE PATIENT

2 DETERMINE THE NUMBER OF VIALS NEEDED

Weight	less than 25 kg	26-50 kg	51-75 kg	76-100 kg
60 mg vial	1	2	3	4

3 RECONSTITUTE

■ Activate the drug: artesunate powder + bicarbonate ampoule (immediately before use)

4 DILUTE

■ Reconstituted artesunate + saline solution (or dextrose 5%)

■ Volume for dilution

	IV	IM
Bicarbonate solution volume	1 ml	1 ml
Saline solution volume	5 ml	2 ml
Total volume	**6 ml**	**3 ml**
Artesunate 60 mg solution concentration	10 mg/ml	20 mg/ml

IMPORTANT

Water for injection is not an appropriate dilutant

1. World Health Organization (WHO) List of Prequalified Medicinal Products (http://apps.who.int/prequal/query/ProductRegistry.aspx?list=any) artesunate injectable, reference N° MA061, prequalified on 05-Nov-2010.
2. World Health Organization, Management of Severe Malaria - A practical handbook - Third edition - April 2013 - (http://www.who.int/malaria/publications/atoz/9789241548526/en/index.html)

5 CALCULATE THE DOSE

■ Calculate and withdraw the required dose in ml according to route of administration:

Less than 20 kg

For intravenous route (IV)
Concentration: 10 mg/ml

3.0 mg x body weight (kg) ÷ IV artesunate solution concentration 10 mg/ml
Round up to the next whole number

Example:
Dose needed (ml) for 8 kg child:
3.0 x 8 / 10 = 2.4 ml
2.4 ml rounded up to 3 ml

Weight kg	Dose mg	Dose ml
6 - 7	20	2
8 - 10	30	3
11 - 13	40	4
14 - 16	50	5
17 - 20	60	6

For intramuscular route (IM)
Concentration: 20 mg/ml

3.0 mg x body weight (kg) ÷ IM artesunate solution concentration 20 mg/ml
Round up to the next whole number

Example:
Dose needed (ml) for 8 kg child:
3.0 x 8 / 20 = 1.2 ml
1.2 ml rounded up to 2 ml

Weight kg	Dose mg	Dose ml
6 - 7	20	1
8 - 10	30	2
11 - 13	40	2
14 - 16	50	3
17 - 20	60	3

More than 20 kg

Concentration: 10 mg/ml

2.4 mg x body weight (kg) ÷ IV artesunate solution concentration 10 mg/ml
Round up to the next whole number

Example:
Dose needed (ml) for 26 kg child:
2.4 x 26 / 10 = 6.24 ml
6.24 ml rounded up to 7 ml

Weight kg	Dose mg	Dose ml
20 - 25	60	6
26 - 29	70	7
30 - 33	80	8
34 - 37	90	9
38 - 41	100	10
42 - 45	110	11
46 - 50	120	12
51 - 54	130	13
55 - 58	140	14
59 - 62	150	15
63 - 66	160	16
67 - 70	170	17
71 - 75	180	18
76 - 79	190	19
80 - 83	200	20
84 - 87	210	21
88 - 91	220	22
92 - 95	230	23
96 - 100	240	24

Concentration: 20 mg/ml

2.4 mg x body weight (kg) ÷ IM artesunate solution concentration 20 mg/ml
Round up to the next whole number

Example:
Dose needed (ml) for 26 kg child:
2.4 x 26 / 20 = 3.12 ml
3.12 ml rounded up to 4 ml

Weight kg	Dose mg	Dose ml
20 - 25	60	3
26 - 29	70	4
30 - 33	80	4
34 - 37	90	5
38 - 41	100	5
42 - 45	110	6
46 - 50	120	6
51 - 54	130	7
55 - 58	140	7
59 - 62	150	8
63 - 66	160	8
67 - 70	170	9
71 - 75	180	9
76 - 79	190	10
80 - 83	200	10
84 - 87	210	11
88 - 91	220	11
92 - 95	230	12
96 - 100	240	12

Remark: the upper limit for each weight band is 0.9 kg e.g. 14 - 16 kg covers 14 - 16.9 kg.

6 ADMINISTER

7 DOSING SCHEDULE

1. Give **3 parenteral doses** over 24 hours as indicated in the opposite table

2. Give **parenteral doses** for a minimum of 24 hours once started irrespective of the patients ability to tolerate oral treatment earlier.

- **Day 1** Dose 1: on admission (0 Hours)
  Dose 2: 12 hours later
- **Day 2** Dose 3: 24 hours after first dose

- When the patient can take oral medication, prescribe a full 3-day course of recommended first line oral Artemisinin Combination Therapy (ACT).
  The first dose of ACT should be taken between 8 and 12 hours after the last injection of artesunate.
- Until the patient is able to take oral medication, continue parenteral treatment (one dose a day) for a maximum of 7 days.
- A course of injectable artesunate should always be followed by a 3-day course of ACT.

- Evaluate the patient's progress regularly.

IMPORTANT

- Prepare a fresh solution for each administration.
- Discard any unused solution after use.

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10.7.3 MALARIA, PROPHYLAXIS (SELF-PROVIDED CARE)

Z29.1

DESCRIPTION

In South Africa, malaria prophylaxis should be used, together with preventive measures against mosquito bites, from September to May in high-risk areas. It is recommended that persons intending to travel to high-risk areas take the relevant prophylactic therapy. Prophylactic therapy must be started before entering the malaria area, and continued for a period of time after exiting the malaria area.

GENERAL MEASURES

Always use preventative measures, in addition to pharmacological therapy, against mosquito bites between dusk and dawn:

» Use di-ethyl 3-methylbenzamid (DEET) insecticide impregnated mosquito nets, insecticide coils or pads.
» Apply insect repellent to exposed skin and clothing. Aim for 30% DEET. Don't get on lips, eyes, breaks in skin.
» Wearg long sleeves, long trousers and socks, if outside, as mosquitoes are most active at this time.
» Visit endemic areas only during the dry season.

MEDICINE TREATMENT

Prophylaxis

CAUTION

Immunocompromised patients, pregnant women and children <8 years of age should avoid visiting malaria-endemic areas, as they are more prone to the serious complications of malaria.

However, if this cannot be avoided, self-provided malaria chemoprophylaxis should be considered (as recommended by the National Department of Health Malaria Treatment Guidelines)

Non-pregnant adults:

- Doxycycline oral, 100 mg daily.
  - Take from 2 days prior to entering endemic area until 4 weeks after exiting the endemic area.

LoE:IIIb[4]

Children ≥8 years of age:

- Doxycycline oral, 2 mg/kg/dose daily.
  - Take from 2 days prior to entering endemic area until 4 weeks after exiting the endemic area.

LoE:IVb[5]

Note: Doxycycline is contra-indicated in pregnant women, and in children <8 years of age.

10.8 MEASLES

B05.0-4/B05.8-9

Note: notifiable medical condition.

CASE DEFINITION

» Fever.

AND

» Red maculopapular (blotchy) rash.

AND

» Cough or coryza (runny nose) or conjunctivitis.

Inform the local EPI co-ordinator about all cases of suspected measles, (i.e. which fulfil the case definition criteria). Send clotted blood and throat swabs to confirm (or exclude) a diagnosis of measles.

DESCRIPTION

A viral infection that is especially dangerous in malnourished children or in children who have other diseases such as TB or HIV/AIDS.

Initial clinical features, that occur 7–14 days after contact with an infected individual, include:

» coryza
» fever
» diarrhoea
» conjunctivitis which may be purulent
» cough

After 2–3 days of the initial clinical features, a few tiny white spots, like salt grains appear in the mouth (Koplik spots).

The skin rash appears 1–2 days later, lasting about 5 days and:

» usually starts behind the ears and on the neck
» then on the face and body
» thereafter, on the arms and legs

Secondary bacterial infection (bronchitis, bronchopneumonia, and otitis media) may occur, especially in children with poor nutrition or other concomitant conditions.

GENERAL MEASURES

» Isolate the patient in the clinic to prevent spread.
» In the clinic use face masks and gloves when examining the patient.
» Counsel the caregiver to isolate the patient in the home (if feasible).
» Reduce exposure of children < 12 months of age and pregnant women to the index patient.
» Ensure that the caregiver and other close contacts have been previously immunised.

MEDICINE TREATMENT

All children < 5 years of age with measles should be given an extra dose of vitamin A, unless the last dose was received within a month:

- Vitamin A (retinol), oral, as a single dose.

Age range	**Dose** units	**Capsule** 100 000 IU	**Capsule** 200 000 IU
Infants 6–11 months	100 000	1 capsule	–
Children 12 months–5 years	200 000	2 capsules	1 capsule

In children < 5 years of age, give the 1st dose immediately. If the child is sent home, the caregiver should be given a 2nd dose to take home, which should be given the following day.

Administration of a vitamin A capsule
- Cut the narrow end of the capsule with scissors.
- Open the child's mouth by gently squeezing the cheeks.
- Squeeze the drops from the capsule directly into the back of the child's mouth. If a child spits up most of the vitamin A liquid immediately, give one more dose.

For fever with distress:

Children
- Paracetamol, oral, 10–15 mg/kg/dose 6 hourly when required. See dosing table, pg 23.8.

Adults
- Paracetamol, oral, 1 g 4–6 hourly when required.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4 g in 24 hours.

Children with diarrhoea:
Treat according to Section 2.9.1: Acute diarrhoea in children.

Children with pneumonia (1st dose before referral):
- Amoxicillin, oral, 45 mg/kg/dose. See Section 17.3.4.1: Pneumonia in children.

Children with otitis media:
- Amoxicillin, oral, 45 mg/kg/dose. See Section 19.4.2 Otitis media, acute.

Pneumonia or otitis media with severe penicillin allergy:
Z88.0

Children
- Macrolide, e.g.:
- Azithromycin, oral, 10 mg/kg/dose daily for 3 days. See dosing table, pg 23.2. *LoE:IVb*[6]

Purulent conjunctivitis:
- Chloramphenicol, 1%, ophthalmic ointment 8 hourly into lower conjunctival sac.

REFERRAL
» All adults.
» Children <6 months of age.
» Children who are malnourished or immunocompromised, or who have TB.
» Where serious complications are present. These include:
  - stridor/croup
  - pneumonia
  - dehydration
  - neurological complications
  - severe mouth and eye complications

Provide emergency treatment, if needed, before referral.

10.9 MENINGITIS

See Chapter 15: Central nervous system.

10.10 MUMPS

B26.0-3/B26.8-9

DESCRIPTION

Incubation period: 14–21 days.
A viral infection primarily involving the salivary glands.
Signs and symptoms:
» Fever.
» Pain on opening the mouth or eating.
» About two days later a tender swelling appears below the ears at the angle of the jaw, often first on one side and later on the other. The swelling disappears in about 10 days.

GENERAL MEASURES

» Bed rest during febrile period.
» Advise on oral hygiene.
» Recommend plenty of fluids and soft food during acute stage.
» Patient is infectious from 3 days before parotid swelling to 7 days after it started. Isolate until swelling subsides.
» Children may return to school 1 week after initial swelling.

MEDICINE TREATMENT

Children

- Paracetamol, oral, 10–15 mg/kg/dose 6 hourly when required. See dosing table, pg 23.8.

Adults

- Paracetamol, oral, 1 g 4–6 hourly when required.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4 g in 24 hours.

REFERRAL

» Abdominal pain (to exclude pancreatitis).
» Painful swollen testes (orchitis).
» Suspected meningo-encephalitis.

10.11 RUBELLA (GERMAN MEASLES)

B06.0/B06.8-9

DESCRIPTION

Incubation period: 14–21 days. A viral infection with skin lesions that is less severe than measles and lasts only 3–4 days.

A maculopapular red rash starts on the face spreading to the trunk, arms, and legs. It usually fades as it spreads.

Note: If cough, coryza or conjunctivitis are also present, it is essential to exclude measles. See case definition of measles (Section 10.8: Measles).

Clinical features include:
» mild rash.
» swollen and tender lymph nodes behind the ears or at the back of the neck(suboccipital).
» in adults, a small joint arthritis may occur.

Note: Infection during the first or second trimester of pregnancy may lead to severe permanent deformities in the baby. All pregnant women should be referred for confirmation of diagnosis of rubella and counselling.

GENERAL MEASURES
» Bed rest, if needed.
» Isolate from pregnant women for 7 days after onset of the rash.

MEDICINE TREATMENT
Children
- Paracetamol, oral, 10–15 mg/kg/dose 6 hourly when required. See dosing table, pg 23.8.

Adults
- Paracetamol, oral, 1 g 4–6 hourly when required.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4 g in 24 hours.

REFERRAL
Urgent
» Pregnant women with rubella.
» Pregnant women who have been in contact with a patient with rubella.

10.12 SCHISTOSOMIASIS (BILHARZIA)
B65.0-3/B65.8-9
Note: notifiable medical condition.

DESCRIPTION
A parasitic infestation with:
» *Schistosoma haematobium*: primarily involves the bladder and renal tract, or
» *Schistosoma mansoni:* primarily involves the intestinal tract.

Infestation occurs during washing, bathing or paddling in water harbouring snails shedding this parasite.

Clinical features vary with the location of the parasite.

Most cases are asymptomatic.

Chronic schistosomiasis may present with local or systemic complications due to fibrosis, including urinary tract obstruction with ensuing renal failure, portal hypertension or other organ involvement.

	Schistosoma haematobium	***Schistosoma mansoni***
Clinical features	» blood in the urine » recurrent cystitis » other urinary symptoms	» diarrhoea with blood and mucus in the stools » colicky abdominal pain » enlarged liver and spleen
Diagnosis	» eggs in urine or stool on microscopy	» eggs in urine or stool on microscopy, rectal biopsy

Table 10.2: Differences between *Schistosoma haematobium* and *Schistosoma mansoni*

Acute schistosomiasis occurs several weeks after exposure and may present with non-specific signs such as fever, cough, headache, and urticaria.

Life threatening cardiac and neurological complications may occur.

Refer all suspected cases for diagnosis and further management.

Diagnosis is made by assessing for eosinophilia and conducting serological testing.

GENERAL MEASURES

If bilharzia is endemic, educate the community to avoid contact with contaminated water:
» Do not urinate or pass stools near water used for drinking, washing or bathing.
» Do not swim in contaminated water.
» Collect water from rivers and dams at sunrise when risk of infestation is lowest.
» Boil all water before use.

MEDICINE TREATMENT

In endemic areas where urine microscopy cannot be done patients should be treated empirically after first excluding possible glomerulonephritis, i.e. no raised blood pressure, no oedema, and no shortness of breath. See Section 8.3: Glomerular diseases (GN).

In non-endemic areas treatment should be given only if eggs of *S. haematobium* or *S. mansoni* are found in the urine/faeces.

Children

- Praziquantel, oral, 40 mg/kg as a single dose. See dosing table pg 23.8.

Adults

- Praziquantel, oral, 40 mg/kg as a single dose. *LoE:Ia*[7]

Note: Praziquantel may cause life-threatening deterioration if given in acute schistosomiasis. If the acute phase is suspected, consult with a specialist.

REFERRAL

» Children < 2 years of age.
» Ongoing urinary tract symptoms including haematuria persisting for 60 days after treatment.
» Signs of bleeding disorders or glomerulonephritis.
» Suspected acute schistosomiasis.

10.13 SHINGLES (HERPES ZOSTER)

B02.0-3/B02.7-9

DESCRIPTION

Dermatomal eruption of vesicles on an erythematous base due to varicella zoster virus (lies dormant in nerve ganglia following chickenpox).

GENERAL MEASURES

» Isolate patient from immunocompromised or pregnant non-immune individuals (who may develop severe chickenpox).
» Offer HIV test, especially to patients.

MEDICINE TREATMENT

Antiviral therapy, indicated for herpes zoster:

» in immunocompetent individuals - only of benefit within 72 hours of onset, and
» in immunocompromised patients - beyond 72 hours, provided that there are active lesions.

Adults:

- Antiviral, (active against herpes zoster) e.g.:
- Aciclovir, oral, 800 mg five times daily for 7 days (4 hourly missing the middle of the night dose). *LoE:Ia*[8]

For pain:

Pain is often very severe and requires active control. A combination of different classes of analgesics is often necessary.

- Paracetamol, oral, 1 g 4–6 hourly when required.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4 g in 24 hours.

AND/OR *LoE:IVb*[9]

During acute presentation if pain is severe and not adequately controlled:

- Tramadol, oral 50 mg 6 hourly (Doctor prescribed).
  - If response not adequate, increase dose to 100 mg 6 hourly. *LoE:IVb*[10]

To treat post-herpetic neuralgia:

Initiate treatment with adjuvant therapy early.

- Amitriptyline, oral, 25 mg at night (Doctor prescribed).
  - Titrate as necessary to a maximum of 75 mg. *LoE:IVb*[11]

REFERRAL

» Herpes zoster with secondary dissemination or neurological involvement.
» Ocular involvement (if the tip of the nose is involved then ocular involvement is more likely).
» Uncontrolled pain.
» All children.

10.14 TICK BITE FEVER

A77.1/A79.8/A79.9

DESCRIPTION

Tick-borne infection due to *Rickettsia conorii*, acquired from dogs, or *Rickettsia africae*, acquired from cattle and game. The hallmark of tick bite fever is the eschar, i.e. round black lesion ± 5 mm in diameter with an inflammatory halo. A rash develops on about the third day of illness in about two thirds of patients with *R. conorii* and in fewer cases of *R. africae* infection. In *R. conorii* infection the rash is maculopapular and involves the palms and soles. In *R. africae* infection the rash is sparse and may be vesicular. The classic triad of fever, eschar, and rash occurs in 50-75% of patients. Signs of severe tick bite fever include severe headache, hypotension, shortness of breath, and neurological manifestations.

GENERAL MEASURES

» Application of insect repellent to exposed skin and clothing.
» Wearing long sleeves, long trousers, and socks, if outside.
» Inspect clothing for presence of ticks after suspected exposure.

Complications include:

» vasculitis
» encephalitis
» thrombosis
» renal failure
» myocarditis
» pneumonitis
» thrombocytopaenia

MEDICINE TREATMENT

Antibiotic therapy:

Treatment must be started before confirmation of diagnosis by serology.
Although not recommended for children < 8 years of age, doxycycline is still regarded as the medicine of choice for children with tick bite fever. However, due to the unavailability of lower dosage forms of doxycycline alternative medicines are considered in children < 8 years of age or those weighing < 45kg with mild infection.

Mild to moderate infection:

Children < 45 kg

- Azithromycin, oral, 10 mg/kg/dose daily for 3 days. See dosing table pg 23.2. *LoE:IIIb*[12]

Children ≥ 45 kg and adults

- Doxycycline, oral, 100 mg 12 hourly, for at least 3 days after the fever subsides with clinical improvement.
  - Maximum duration of treatment is 7 days. *LoE:IIIb*[13]

In pregnancy:

- Doxycycline, oral, 100 mg 12 hourly for 2 days.

Then switch to:

- Azithromycin, oral, 500 mg 12 hourly for 3 days. *LoE:IVb*[14]

For headache and fever:

Children

- Paracetamol, oral, 15 mg/kg/dose, 6 hourly as required. See dosing table, pg 23.8. *LoE:IVb*[15]

Adults

- Paracetamol, oral, 1 g 4–6 hourly when required.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4 g in 24 hours *LoE:IVb*[16]

REFERRAL

» Patients unable to take oral therapy.
» Patients not responding to adequate therapy, e.g. fever persisting for > 48 hours after initiation of treatment.
» Patients with complications.
» Patients with severe tick bite fever.

10.15 TYPHOID FEVER

See Section 2.13: Typhoid fever.

10.16 TUBERCULOSIS

See Chapter 17: Respiratory conditions. Section 17.4: Pulmonary tuberculosis.
Note: notifiable medical condition.

10.17 TUBERCULOSIS, EXTRAPULMONARY

A18.0-8
Note: notifiable medical condition.

DESCRIPTION

Extra-pulmonary tuberculosis is defined as infection of organ systems other than the lung with Mycobacterium tuberculosis. Extra-pulmonary TB can present with non-specific symptoms such as unintentional weight loss (> 1.5 kg in a month), night sweats, and fever for more than 2 weeks. Other symptoms depend on the organ affected. The most common types of extra-pulmonary TB are listed below along with commonly associated signs and symptoms:

Extra-pulmonary TB type	Common presenting sign/symptom
TB lymphadenitis	» Audible wheeze or typical brassy cough caused by large mediastinal lymph nodes. » Peripheral TB lymphadenopathy occurs in neck and armpits. Typically nodes are large (> 2 cm), tender, non-symmetrical, matted, firm to fluctuant and rapidly growing.
TB pleural effusion (usually single-sided)	» Non-productive cough. » Chest pain. » Shortness of breath. » High temperature.

	» Tracheal and mediastinal shift away from the side of the effusion. » Decreased chest movement. » Stony dullness on percussion on the side of the effusion.
TB of spine, bones and joints	» Decreased movement in the joints. » Excessive sweating, especially at night. » Joint swelling with warm, tender joints. » Low-grade fever. » Muscle atrophy and/or spasms. » Numbness, tingling, or weakness below the infection (if the spine is involved).
TB pericardium	» Chest pain. » Shortness of breath. » Dizziness and weakness from low cardiac output » Signs and symptoms of right-sided heart failure (tachycardia, low BP, peripheral oedema, liver congestion, ascites).
TB meningitis	» During the early phase of TB meningitis, malaise, low-grade fever, headache and personality change may be present. » With suspected established infection assess for: – gradual onset of headache – malaise – confusion – decreased consciousness – vomiting – neck stiffness and positive Kernig's sign » In children, TB meningitis may be acute, sub-acute or chronic and typically presents between 23-49 months of age with: – altered level of consciousness – history of fever – irritability – headache – convulsions – poor feeding and failure to thrive – vomiting – cough – meningism
Disseminated/miliary TB	» Most often seen in children and young adults. » Fever. » Cough. » Generalised lymphadenopathy. » Hepatomegaly. » Consider in febrile patients presenting with HIV wasting syndrome.
TB empyema	» Similar to pleural effusion, but aspiration reveals thick pus.
TB peritoneum	» Ascites with no signs of portal hypertension. » Possible palpable abdominal masses. » Possible bowel obstruction.

Table 10.3: Types of extra-pulmonary TB

REFERRAL

All suspected cases of extra-pulmonary TB should be referred immediately to secondary or tertiary care for diagnosis and further management.

10.18 VIRAL HAEMORRHAGIC FEVER (VHF)

A98.0-5/ A98.8/A99/A91

Note: notifiable medical conditions.

Consult the most recent Viral Haemorrhagic Fever Guidelines from the National Department of Health.

DESCRIPTION

Viral haemorrhagic fevers (VHF) are uncommon conditions in South Africa. They may present with non-specific signs or with signs strongly suggestive of VHF (Table 10.4). Other symptoms and organ involvement may be variable.

Signs strongly suggesting VHF	Non-specific signs that may occur with VHF
» Petechial rash. » Ecchymoses. » Other haemorrhagic signs (e.g. epistaxis, haematemesis, melaena). » Non-specific signs of infection.	» Fever. » Headache. » Conjuctivitis. » Pharyngitis. » Myalgia (especially lower back pain). » Vomiting. » Abdominal pain. » Diarrhoea.

Table 10.4: Signs and symptoms of viral haemorrhagic fevers (VHF)

More than 90% of suspected cases of VHF in South Africa prove to be severe forms of common diseases. Many of the diseases mistaken for VHF are treatable if diagnosed early.

These include:

- Severe tick bite fever.
- Severe falciparum malaria.
- Severe bacterial infections, particularly *N.meningitidis*.
- Fulminant hepatitis.
- Leptospirosis.

Endemic causes of VHF in South Africa are Crimean-Congo fever and Rift Valley Fever, both of which may be transmitted between humans by means of blood and body fluids. Imported conditions include Lassa, Ebola and Marburg Fever amongst others.
Obtaining a history of possible exposure to infection (including a detailed travel history) is crucial to diagnosing VHF. Relatives and friends often provide more reliable information than severely ill patients.

GENERAL MEASURES

All suspected, probable VHF cases and contacts of VHF cases must be discussed and managed in consultation with the Regional Virologist or Infectious Diseases Consultant at the referral centre.

Cases should also be discussed with the Special Pathogens Unit of the National Institute for Communicable Diseases (NICD):

Tel: 011 386 6000, Outbreak hotline: 082 883 9920

Transfer of patients will only occur once all relevant arrangements have been made to limit further exposure to a potentially contagious and life threatening agent.

Viral haemorrhagic fevers (VHF) are readily transmitted to healthcare workers, so it is essential to apply strict contact precautions.
ISOLATE ALL SUSPECTED SYMPTOMATIC CASES AT ALL TIMES

If VHF is considered, isolate patient in a single room and take proper precautions to limit further exposure. These include where available:
» long-sleeved disposable gown,
» waterproof apron if the patient is bleeding,
» two pairs of latex gloves, one underneath the gown and one with the wrist of the glove pulled over the gown cuff,
» disposable face mask (preferably with a visor),
» goggles if a mask without the visor is used,
» waterproof boots or 2 pairs of overshoes, one over the other.

Note: Do not touch your own skin with your gloved hands.

MANAGEMENT

Management of VHF contact
» Consult clinician, discuss with NICD and isolate patient (See above).
» Record and follow-up all patient contacts.

Management of suspected/possible/probable VHF
» Non-specific signs:
  - Consult with clinician, discuss with NICD, isolate patient, initiate ceftriaxone and record and follow-up all patient contacts.
» Signs strongly suggestive of VHF:
  - Consult with a clinician, discuss with NICD, isolate patient, initiate ceftriaxone and arrange transfer with EMS (providing patient's VHF status, and names, addresses and telephone numbers of patient contacts).

Adults
- Ceftriaxone, IV, 2 g immediately. *LoE:IVb*[17]

Children
- Ceftriaxone, IM, 80 mg/kg/dose immediately as a single dose. See dosing table, pg 23.3.
  - Do not inject more than 1 g at one injection site.

CAUTION: USE OF CEFTRIAXONE IN NEONATES AND CHILDREN
» If *SUSPECTING SERIOUS BACTERIAL INFECTION* in neonate, give ceftriaxone, even if jaundiced.
» Avoid giving calcium-containing IV fluids (e.g. Ringer Lactate) together with ceftriaxone:
  - If ≤ 28 days old, avoid calcium-containing IV fluids for 48 hours after ceftriaxone administered.

- If > 28 days old, ceftriaxone and calcium-containing IV fluids may be given sequentially provided the giving set is flushed thoroughly with sodium chloride 0.9% before and after.
- Preferably administer IV fluids without calcium contents.

» Always include the dose and route of administration of ceftriaxone in the referral letter.

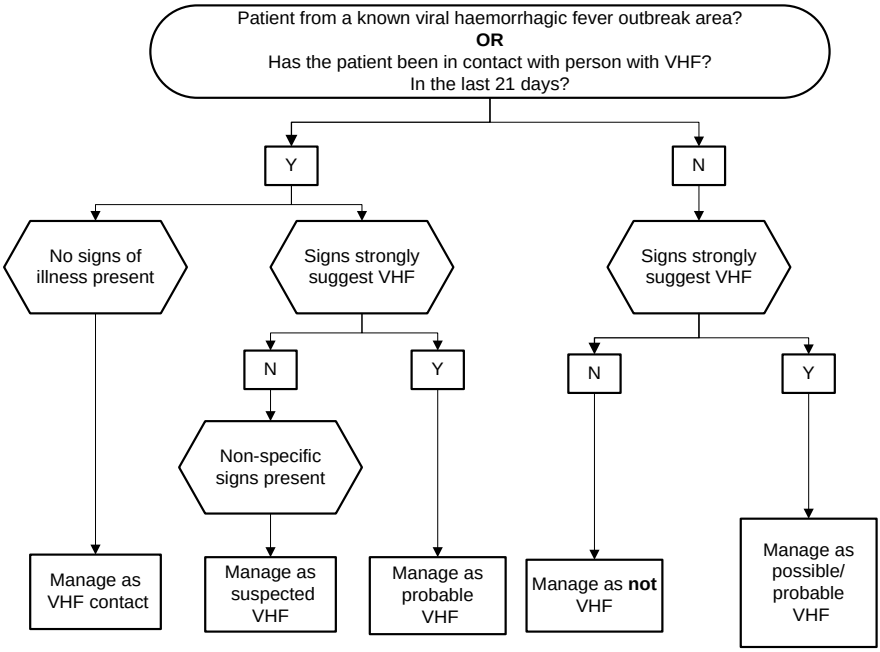

Figure 10.2: Algorithm for management of VHF

REFERRAL

» All cases, after consultation with clinician, discussion with NICD, isolation of patient and management of acute condition.

Manage all contacts of VHF cases according to the current national guidelines. Ensure that contact details are obtained and that there is a plan to manage contacts.

10.19 EMERGING RESPIRATORY PATHOGENS, E.G. COVID-19: CORONAVIRUS DISEASE-19; MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS INFECTION: MERS COV

Note: notifiable medical conditions.

Consult the most recent guidelines from the National Department of Health or NICD.

DESCRIPTION

Viral respiratory illness caused by coronaviruses, including Middle East respiratory syndrome (MERS-CoV), severe acute respiratory syndrome (SARS), and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). SARS-CoV-2 causes coronavirus infectious disease-2019 (COVID-19).

Individuals present with a wide spectrum of clinical presentations ranging from asymptomatic infection to acute upper respiratory illness, and rapidly progressing lower respiratory illness; respiratory failure, septic shock and multi-organ failure resulting in death.

A typical presentation includes:
» fever (>38°C), chills or rigors, cough, shortness of breath
Presentation may include:
» hemoptysis, sore throat, myalgias, diarrhoea, vomiting, abdominal pain

Complications:

» severe pneumonia
» acute respiratory distress syndrome (ARDS)
» acute renal failure
» refractory hypoxaemia

GENERAL MEASURES

All suspected, probable cases and contacts must be discussed and managed in consultation with the regional virologist or infectious diseases specialist at the referral centre. Transfer of patients will only occur once all relevant arrangements have been made to limit further exposure to a potential contagious and life threatening agent.
Droplet precautions should be added to the standard precautions. Airborne precautions should be applied when performing aerosol-generating procedures.

Isolate suspected symptomatic cases at all times.

Management
Treatment
Treatment is supportive.
No antiviral agents are currently available.
Management of contact: consult with NICD and isolate contact.
Record and follow-up all patient contacts.

Prevention
Handwashing and the careful disposal of materials infected with nasal secretions.
Antiseptic/disinfectant solutions: choroxylenol, benzalkonium chloride, and cetrimide.
Chlorhexidine has been shown to be ineffective.

REFERRAL

All cases, after consultation with infectious diseases and NICD.

10.19.1 COVID-19: CORONAVIRUS DISEASE-19

U07.1/U07.2
Note: notifiable medical condition.

Consult the most recent guidelines on the clinical management of suspected or confirmed Covid-19 disease available at:
https://www.knowledgehub.org.za/content/covid-19

DESCRIPTION

» Viral respiratory illness caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).
» The mean incubation period is 4-5 days but may be up to 14 days. Patients may however be infectious for 2-3 days prior to the onset of symptoms.
» The elderly are at high risk for severe COVID-19 disease. Other risk factors include cardiopulmonary comorbidities, uncontrolled diabetes mellitus, obesity, TB, HIV, mental illness and substance use disorders. *LoE:IIIb*[18]
» COVID-19 presents as an asymptomatic infection; or as a respiratory tract infection that may range from mild to severe, with atypical manifestations such as diarrhoea, skin manifestations, hyperglycaemic syndromes, and large vessel strokes.

» A suspected COVID-19 case includes any person presenting with an acute (≤14 days) respiratory tract infection or other clinical illness compatible with COVID-19, or an asymptomatic person who is a close contact to a confirmed case.
» In the context of COVID-19, the key respiratory syndrome consists of ANY of:
  - Cough
  - Sore throat
  - Shortness of breath
  - Anosmia (loss of smell) or dysgeusia (loss of taste)
» This may present with or without other symptoms (such as fever, weakness, myalgia or diarrhoea).

» Complications include refractory hypoxaemia, acute respiratory distress syndrome (ARDS), long-COVID and multisystem inflammatory syndrome in children (MIS-C) and in adults (MIS-A).

Testing

» Rapid antigen tests or PCR-based tests are both acceptable options to use for diagnosis. Rapid antigen tests may be performed on all patients for whom the PCR test is indicated in situations where no PCR tests are available, or when the PCR turnaround time limits the clinical or public health response utility.
» Upper respiratory tract (nasopharyngeal or oropharyngeal) samples should be sent on all patients. Sputum can be sent when available.
» A single positive rapid or PCR test is sufficient proof of COVID-19 infection.
» A negative rapid test should be followed up by a PCR test if the patient has symptoms compatible with COVID or if the patient has had a recent exposure to a confirmed case.
» Due to poor sensitivity within the first 1-2 weeks after symptom onset, serology (antibody test) is not recommended for the diagnosis of acute COVID-19 infection.
» All healthcare workers should wear appropriate personal protective equipment (PPE) for both contact and respiratory precautions when obtaining specimens
» Record and report and notify all confirmed COVID-19 cases. *LoE:IVb*[19]

GENERAL MEASURES

» Manage patients who are asymptomatic or who meet criteria for mild disease at home, provided they can safely self-isolate and seek urgent health care if required.
» Give strict advice to patients who self-isolate at home and how to reduce possible transmission to others.

Criteria for management at home (for age >12 years):

Mild disease:

» SpO2 ≥95%
» Respiratory rate <25 breaths/minute
» HR <120 beats/minute
» Mental status normal

Able to safely self-isolate:

» Separate bedroom available for patient to self-isolate in
» Able to maintain physical distancing at home
» Able to maintain hand hygiene
» Patient able to contact, and return to, healthcare facility in case of progression to severe disease

MEDCINE TREATMENT

Note: Antibiotics are of no value for the treatment of confirmed COVID-19, unless there is clear evidence of a coexisting infection.

Paracetamol is recommended for symptomatic treatment of patients with pain in preference to nonsteroidal anti-inflammatory drugs (NSAIDs).

Children

- Paracetamol, oral, 10–15 mg/kg/dose 6 hourly when required. See dosing table, pg 23.8.

Adults

- Paracetamol, oral, 1 g 4–6 hourly when required.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4 g in 24 hours.

Note:

» Any deterioration in the ability to perform activities of daily living at home as a result of dyspnoea should prompt re-evaluation at a healthcare facility.
» Corticosteroids should not be used for the treatment of COVID-19 in patients who do not require supplemental oxygen or mechanical ventilation, unless they are required for another reason such as an acute exacerbation of asthma or chronic obstructive pulmonary disease.

COVID-19 HOTLINE NUMBER
0800029999
http://www.nicd.ac.za/ ; https://sacoronavirus.co.za/

» Practice hand hygiene.
» Use healthcare worker PPE: gloves, gown (or apron), and a medical mask.
» Practice safe waste management.
» Use either disposable or dedicated equipment (e.g. stethoscopes, blood pressure cuffs and thermometers). If equipment needs to be shared among patients, clean and disinfect between each patient use.
» Limit patient movement within the institution and ensure that patients wear medical masks when outside their rooms.

Comprehensive national IPC guidelines for COVID-19 are available at: https://www.knowledgehub.org.za/content/covid-19

REFERRAL

Urgent

Refer cases urgently where there is a respiratory rate of >25 breaths/minute, SpO2 <94% in patients breathing room air or oxygen, heart rate of >120 beats/minute, are confused, agitated or have decreased consciousness. Administer oxygen and monitor oxygen saturation during referral. If unsure, consult with ID expert or NICD (see above).

LoE:IIIb[20]

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Doxycycline (pregnancy – tick bite fever): McGready R, Prakash JA, Benjamin SJ, Watthanaworawit W, Anantatat T, Tanganuchitcharnchai A, et al. Pregnancy outcome in relation to treatment of murine typhus and scrub typhus infection: a fever cohort and a case series analysis. PLoS Negl Trop Dis. 2014 Nov 20;8(11):e3327. https://pubmed.ncbi.nlm.nih.gov/25412503/

Doxycycline (pregnancy – tick bite fever): South African Medicines Formulary. 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

Doxycycline (pregnancy – tick bite fever): Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer SM, Gideon PS, et al. Antibiotics potentially used in response to bioterrorism and the risk of major congenital malformations. Paediatr Perinat Epidemiol. 2009 Jan;23(1):18-28. https://pubmed.ncbi.nlm.nih.gov/19228311/

[15] Paracetamol, oral (children - headache and fever in tick bite fever): National Department of Health, Essential Drugs Programme: Paediatric Hospital Level STGs and EML, draft. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[16] Paracetamol, oral (adults - headache and fever in tick bite fever): National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, draft. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[17] Ceftriaxone, IM (adults): National Department of Health. National guidelines for recognition & management of viral haemorrhagic fevers, 2019. https://www.knowledgehub.org.za/

[18] Risk factors for COVID-19: National Department of Health. Clinical management of suspected or confirmed COVID-19 disease version 6 (September 2021). https://www.knowledgehub.org.za/elibrary/clinical-management-suspected-or-confirmed-covid-19-disease

Risk factors for COVID-19: Mendelson M, Boloko L, Boutall A et al. Clinical management of COVID-19: Experiences of the COVID-19 epidemic from Groote Schuur Hospital, Cape Town, South Africa. S Afr Med J 2020;110(10):973-981. https://doi.org/10.7196/SAMJ.2020.v110i10.15157

Risk factors for COVID-19: Li L, Li F, Fortunati F, Krystal JH. Association of a Prior Psychiatric Diagnosis With Mortality Among Hospitalized Patients With Coronavirus Disease 2019 (COVID-19) Infection. JAMA Netw Open. 2020 Sep 1;3(9):e2023282. https://pubmed.ncbi.nlm.nih.gov/32997123/

[19] Antigen and PCR tests (COVID-19): National Department of Health. Guide to antigen testing for SARS-COV-2 in South Africa, 21 July 2021.

[20] Covid-19: National Department of Health. Clinical management of suspected or confirmed Covid-19 disease Version 6 (September 2021). https://www.knowledgehub.org.za/elibrary/clinical-management-suspected-or-confirmed-covid-19-disease

SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 10: INFECTIONS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020 -2023 REVIEW CYCLE)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG).

All reviews and costing reports may be accessed at: https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

MEDICINE AMENDMENTS:

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED
10.7.2 Malaria, severe/complicated	Quinine, parenteral	Not added as a therapeutic alternative
	Artesunate, parenteral	Retained & dosing amended
10.7.3 Malaria, prophylaxis (self-provided care)	Doxycycline, oral	Added (for non-pregnant adults & children ≥8 years)
	Atovaquone-proguanil, oral	Not added
	Mefloquine, oral	Not added
NEW: Malaria, reduction in transmission	Primaquine, oral	Not added
10.14 Tick bite fever *- In pregnancy*	Doxycycline	Added as initial therapy
	Azithromycin	Retained
10.19.1: Coronavirus Disease-19 (COVID-19)	Antibiotics	Statement added that antibiotics are of no value for the treatment of confirmed COVID-19, unless there is clear evidence of a co-existing infection
	Antigen and PCR tests	Amended to align with NDoH policy
	Referral	Aligned with the Adult Hospital Level COVID-19 STGs in terms of SpO2

10.7.2 MALARIA, SEVERE/COMPLICATED

Quinine, parenteral: *not added as a therapeutic alternative*
Artesunate, parenteral: *retained and dosing amended*
Parenteral quinine was not added as a therapeutic alternative for the management of complicated *Plasmodium falciparum.* Artesunate has a superior effect on mortality compared to quinine RR 0.76 (95% CI 0.65 to 0.9), *(reviewed in previous review cycle).* Artesunate is currently SAHPRA-registered and widely available.

NEMLC also noted with concern reports of quinine being administered for treatment of severe complicate malaria, despite the availability of artesunate (and artesunate has also been added to the medicine tracer list for the PHC ideal clinic/CHC framework).

Level of Evidence: I Systematic review of high certainty[1]

Artesunate, IM dosing
Aligned to 2022 WHO Malaria Guidelines[2] and SAMF[3], based on a pharmacokinetic modelling study[4] that showed that smaller children need higher dosing of intramuscular artesunate.

[1] Artesunate, IV: Artesunate, parenteral: Sinclair D, Donegan S, Isba R, Lalloo DG. Artesunate versus quinine for treating severe malaria. Cochrane Database Syst Rev. 2012 Jun 13;6:CD005967. http://www.ncbi.nlm.nih.gov/pubmed/22696354
[2] WHO Guidelines for malaria, 25 November 2022. Geneva: World Health Organization; 2022 (WHO/UCN/GMP/2022.01 Rev.3). License: CC BY-NC-SA 3.0 IGO.
[3] SAMF, 2022
[4] Hendriksen IC, Mtove G, Kent A, Gesase S, Reyburn H, Lemnge MM, et al. Population pharmacokinetics of intramuscular artesunate in African children with severe malaria: implications for a practical dosing regimen. Clin Pharmacol Ther. 2013 May;93(5):443-50. https://pubmed.ncbi.nlm.nih.gov/23511715/

Level of Evidence: III Pharmacokinetic study

The STG was amended to include the following text:

Children < 20 kg:
- Aresunate IM, 3 mg/kg immediately as a single dose and refer urgently.
  - If transfer to referral hospital is delayed, administer second dose at 12 hours and third dose at 24 hours.

Dosing guidelines developed in collaboration with Medicines for Malaria Venture is recommended for inclusion in the PHC STGs and EML.

10.7.3: MALARIA PROPHYLAXIS

Doxycycline, oral: *added for non-pregnant adults & children ≥8 years*
Atovaquone-proguanil, oral: *not added*
Mefloquine, oral: *not added*

BACKGROUND: Historically, malaria chemoprophylaxis was not considered for inclusion on the national EML, as the NDoH Malaria Programme was not able to provide estimated numbers of travellers requiring prophylaxis in order to determine an estimated budget impact[5]. In addition, a request had been made previously to the Programme to advise of the delivery platform model for malaria chemoprophylaxis. However, recently, the South African Malaria Elimination Committee provided annual case-load reports (2019/2020), to estimate the approximate budgetary investment to provide malaria chemoprophylaxis at primary level of care.

Refer to the medicine review: Malaria chemoprophylaxis, 13 June 2021, below.

Doxycyline as Malaria Prophylaxis_PHC Med

Recommendation: The PHC/Adult Hospital Level Committee suggests that doxycycline be used as malaria chemoprophylaxis in non-pregnant adults.
Rationale: Available evidence shows that doxycycline reduces parasitemia and clinical malaria due to *P falciparum.* Furthermore, mefloquine is currently unavailable in South Africa, and atovaquone-proguanil is unaffordable.
Level of Evidence: Low certainty evidence
Review indicator: Price reduction of atovaquone-proguanil, availability of mefloquine

NEMLC MEETING OF 24 JUNE 2021:

NEMLC Recommendation: The NEMLC accepted the recommendation of doxycycline as malaria chemoprophylaxis as proposed by the PHC/Adult Hospital Level Committee but included children ≥8 years of age[a].
Recommended dosing:
- *Non-pregnant adults:* Doxycycline oral, 100 mg daily, taken from 2 days prior to entering endemic area until 4 weeks after exiting the endemic area.
- *Children ≥ 8 years of age:* Doxycycline oral, 2.2 mg/kg/dose daily, taken from 2 days prior to entering endemic area until 4 weeks after exiting the endemic area.

Note: Pregnant women and children <8 years of age should avoid travelling to endemic areas. However, if this cannot be avoided, self-provided malaria chemoprophylaxis should be considered (as recommended by the National Department of Health Malaria Treatment Guidelines)

[a] SAMF, 2020

The STG was updated, accordingly from:

~~In South Africa, malaria prophylaxis should be used, together with preventive measures against mosquito bites, from September to May in high-risk areas. State facilities do not provide prophylactic therapy. It is recommended that persons intending to travel to high-risk areas take the relevant prophylactic therapy.~~

[5] Minutes of the NEMLC meetings of 2 March 2017, 29 June 2017 and 2 November 2017.

~~**Preventative measures** against mosquito bites between dusk and dawn include:~~
~~» Use of di-ethyl 3-methylbenzamid (DEET) insecticide impregnated mosquito nets, insecticide coils or pads.~~
~~» Application of insect repellent to exposed skin and clothing.~~
~~» Wearing long sleeves, long trousers and socks, if outside, as mosquitoes are most active at this time.~~
~~» Visiting endemic areas only during the dry season.~~

~~**CAUTION**~~
~~Immunocompromised patients, pregnant women and children <5 years of age should avoid visiting malaria-endemic areas, as they are more prone to the serious complications of malaria.~~

~~Refer to National Department of Health Malaria Guidelines.~~

To:

Description
In South Africa, malaria prophylaxis should be used, together with preventive measures against mosquito bites, from September to May in high-risk areas. It is recommended that persons intending to travel to high-risk areas take the relevant prophylactic therapy. Prophylactic therapy must be started before entering the malaria area, and continued for a period of time after exiting the malaria area.

General measures
Always use preventative measures, in addition to pharmacological therapy, against mosquito bites between dusk and dawn include:
» Use of di-ethyl 3-methylbenzamid (DEET) insecticide impregnated mosquito nets, insecticide coils or pads.
» Application of insect repellent to exposed skin and clothing. Aim for 30% DEET. Don't get on lips, eyes, breaks in skin.
» Wearing long sleeves, long trousers and socks, if outside, as mosquitoes are most active at this time.
» Visiting endemic areas only during the dry season.

Medicine treatment
Prophylaxis

CAUTION
Immunocompromised patients, pregnant women and children <8 years of age should avoid visiting malaria-endemic areas, as they are more prone to the serious complications of malaria.
However, if this cannot be avoided, self-provided malaria chemoprophylaxis should be considered (as recommended by the National Department of Health Malaria Treatment Guidelines)

Non-pregnant adults:
- Doxycycline oral, 100 mg daily.
  - Take from 2 days prior to entering endemic area until 4 weeks after exiting the endemic area.

Children ≥8 years of age:
- Doxycycline oral, 2.2 mg/kg/dose daily.
  - Take from 2 days prior to entering endemic area until 4 weeks after exiting the endemic area.

Note: Doxycycline is contra-indicated in pregnant women, and in children <8 years of age.

MALARIA, REDUCTION IN TRANSMISSION

Primaquine, oral: *not added*
Refer to the medicine review: Single, low-dose primaquine to reduce *P. Falciparum* malaria transmission, 25 January 2021.

Primaquine for malaria elimination_Ac

Recommendation: The PHC/Adult Hospital Level Committee proposed that single low-dose primaquine (0.25mg/kg), be added to artemisinin-based treatment for *P. falciparum* malaria, to reduce transmission. Pre-testing for G6PD deficiency is not required unless there is a clinical indication.
Rationale: Evidence of efficacy and safety for SLD primaquine for reducing gametocyte carriage.
Level of Evidence: II Moderate certainty evidence
Review indicator: Evidence of reduced community transmission

HOWEVER, THE NEMLC REVIEWED THE EVIDENCE PRESENTED BY THE PHC/ADULT HOSPITAL LEVEL COMMITTEE AND RECOMMENDED THE FOLLOWING (SEE BELOW):

NEMLC MEETING 25 FEBRUARY 2021:

NEMLC Recommendation: NEMLC acknowledges that there is reasonable evidence showing that primaquine, single dose (SLD), reduces gametocyte carriage. However, there is uncertainty regarding the actual effect on reduction of transmission and malaria eradication *(South African Malaria Elimination Committee was engaged, but no further evidence was forthcoming).* As SAHPRA registration of this product is currently underway, NEMLC recommends that including primaquine SLD on the national EML is premature for use from primary level of care. However, this will be revisited once the product is SAHPRA registered.

Rationale: Routine section 21 access at primary level of care, specifically by nurse prescribers, of an essential medicine is problematic in terms of continuous availability and consistency of price.

Review indicator: Availability of SAHPRA registered primaquine products.

10.14 TICK BITE FEVER

In pregnancy

Doxycycline: *added as initial therapy*

Azithromycin: *retained*

Doxycycline is the antibiotic of choice for the treatment of tick bite fever.[6] However, doxycycline is generally avoided for use in pregnancy, as other tetracyclines have been associated with adverse effects on fetal teeth and bones.[7] A systematic review[8] demonstrated that doxycycline use by these patient groups had a safety profile that differed from that of tetracycline, with no correlation between doxycycline and teratogenic effects during pregnancy or dental staining in children. In addition, a retrospective cohort study suggests that doxycycline (and other antibiotics – azithromycin, ciprofloxacin and amoxicillin) used by pregnant women should not result in a greater incidence of overall major congenital malformations in their infants.[9]

As there is a high fetal risk associated with rickettsial illnesses in pregnancy (higher than in malaria),[10] treatment with doxycycline outweighs the risks and consequences of the side effects associated with doxycycline. Early initiation of empirical doxycycline, to bypass any diagnostic challenges associated with rickettsial infections may likely save lives and prevent severe disease.

The PHC STGs and EML recommends initial treatment with doxycycline for 2 days, followed by azithromycin, for tick bite fever in pregnancy.

STG text was updated as follows:

In pregnancy:

- Doxycycline, oral, 100 mg 12 hourly for 2 days.

Then switch to:

- Azithromycin, oral, 500 mg 12 hourly for 3 days.

Level of Evidence: Very low certainty, conditional recommendation

[6] Frean J, Grayson W. South African Tick Bite Fever: An Overview. Dermatopathology (Basel). 2019 Jun 26;6(2):70-76. https://pubmed.ncbi.nlm.nih.gov/31700846/

[7] SAMF, 2022

[8] Cross R, Ling C, Day NP, McGready R, Paris DH. Revisiting doxycycline in pregnancy and early childhood--time to rebuild its reputation? Expert Opin Drug Saf. 2016;15(3):367-82. https://pubmed.ncbi.nlm.nih.gov/26680308/

[9] Cooper WO, Hernandez-Diaz S, Arbogast PG, Dudley JA, Dyer SM, Gideon PS, et al. Antibiotics potentially used in response to bioterrorism and the risk of major congenital malformations. Paediatr Perinat Epidemiol. 2009 Jan;23(1):18-28. https://pubmed.ncbi.nlm.nih.gov/19228311/

[10] McGready R, Prakash JA, Benjamin SJ, Watthanaworawit W, Anantatat T, Tanganuchitcharnchai A, et al. Pregnancy outcome in relation to treatment of murine typhus and scrub typhus infection: a fever cohort and a case series analysis. PLoS Negl Trop Dis. 2014 Nov 20;8(11):e3327. https://pubmed.ncbi.nlm.nih.gov/25412503/

10.19.1: CORONAVIRUS DISEASE-19 (COVID-19)

Description: A statement was added to the narrative that antibiotics are of no value for the treatment of confirmed COVID-19 unless there is clear evidence of a co-existing infection.

Testing: Guidance on the use of antigen and PCR COVID-19 tests for diagnosis of COVID-19 was aligned with National Department of Health Policy.[11]

Referral: Referral criterion was amended to align with the Adult Hospital Level COVID-19 STGs in terms of SpO2 as follows:

Refer cases urgently where there is a respiratory rate of >25 breaths/minute, SpO2 <~~95%~~ 94% in patients breathing room air or oxygen, heart rate of >120 beats/minute, are confused, agitated or have decreased consciousness. Administer oxygen and monitor oxygen saturation during referral. If unsure, consult with ID expert or NICD (see above).

[11] National Department of Health. Guide to antigen testing for SARS-COV-2 in South Africa, 21 July 2021.

South African National Essential Medicine List
Primary Health Care Medication Review Process
Component: Infections

TITLE: MALARIA PROPHYLAXIS: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

Date: 13 June 2021

Key findings

- The South African Malaria Elimination Committee reported an increase in malaria cases amongst migrant workers traveling home (mostly across borders in malaria-endemic areas), and motivated that malaria chemoprophylaxis be considered for inclusion on the National Essential Medicine List.
- There is no local susceptibility for malaria. However, local resistance to chloroquine and sulfadoxine-pyrimethamine precluded inclusion of these agents from the analysis. Currently, malaria chemoprophylaxis includes atovaquone-proguanil, doxycycline and mefloquine. Disconcertingly, mefloquine has recently been discontinued from the South African market.
- We conducted an evidence review for malaria chemoprophylaxis (mefloquine, atovaquone-proguanil or doxycycline) and one systematic review[8] and 4 RCTs[9-11] were identified.
- **Doxycycline:** A Kenyan study of children[11], 9-14 years, (n=169) that compared various agents against control was reviewed. Doxycycline (n=34) was shown to be 84% effective at preventing parasitaemia (95% CI 66 to 92%); NNT 4 (95% CI 3 to 10), *low certainty evidence;* and 91% effective at preventing clinical malaria (95% CI 61 to 98%) NNT 16 (95% CI 7 to 47), *low certainty evidence*. In this small RCT, mefloquine was also shown to be comparable to doxycycline in preventing asymptomatic (77%; 95% CI 55 to 88%) and symptomatic malaria (81%; 95% CI 44 to 93%), *low certainty evidence*
- **Mefloquine:** A systematic review by Tickell-Painter *et al.,* 2017[8], of 12 RCTs (n=1908) comparing mefloquine to placebo, showed that mefloquine was highly efficacious in reducing clinical cases of malaria (1.4% vs 21.0%; NNT 6, 95% CI 5 to 7; RR 0.09, 95% CI 0.04 to 0.19; I^2=53%), *low certainty evidence.*

  Overall, mefloquine also reduced cases of parasitaemia by 82% (9.8% vs 60.2%; NNT 2, 95% CI 1.7 to 2.3; RR 0.18, 95% CI 0.06 to 0.55; 3 RCTs; n=414; I^2=80%), *low certainty evidence.*

  And, substantially reduced the number of episodes of parasitaemia (8.4% vs 63.3%; NNT 2, 95% CI 1.6 to 2.1; RR 0.05, 95% CI 0.00 to 5.25; 2 RCTs; n=510; I^2=91%), *low certainty evidence.*

  Study heterogeneity was high, but the direction of the effect was consistent across all trials. Of note is that most study participants had a degree of immunity to malaria.

  Mefloquine was also shown to be comparable to doxycycline in preventing symptomatic malaria (4/378 vs 3/366; RR 1.35, 95% CI 0.35 to 5.1; 4 RCTs; n=744; I^2=3%), *low certainty evidence*.
- **Atovaquone-proguanil:** Tickell-Painter *et al.,* 2017[8] also reviewed efficacy of atovaquone-proguanil (n=657) compared to mefloquine (n=636), and reported no clinical cases of malaria with either agent in 2 RCTs, *low certainty evidence*. The authors concluded that *"the absolute risk of malaria during short-term travel appears low with all three established antimalarial agents".*
  Two later RCTs (Ling *et al.,* 2002[10], n=297; Soto *et al.,* 2006[9], n=144) that were not included in the systematic review confirms atovaquone-proguanil's protective efficacy against *Plasmodium falciparum*. The RCTs showed that atovaquone-proguanil reduced parasitaemia, by 96% and 100%, respectively; *low certainty evidence*.
- **Adverse effects:** Tickell-Painter *et al.,* 2017[8], reported that people were less likely to be non-adherent with atovaquone-proguanil compared to mefloquine due to adverse effects *(high-certainty evidence);* but equally as likely to be non-adherent as those taking doxycycline *(low-certainty evidence).*
  Mefloquine users experienced more abnormal dreams, insomnia, anxiety and depressed mood compared to atovaquone-proguanil users *(moderate-certainty evidence)* or doxycyline *(very low-certainty evidence).*
  Doxycycline users were more likely to have dyspepsia, photosensitivity, vomiting, and vaginal thrush *(very low-certainty evidence).*
- **Pregnancy:** General guidance is that pregnant women should avoid travel to malaria-endemic areas. When chemoprophylaxis is required, mefloquine is considered safe for use in the second and third trimesters of pregnancy[13] but globally, guidelines are increasingly recommending use in the first trimester. Doxycycline is avoided due to effects on skeletal development found in animal studies and there is a paucity of safety data in pregnancy for atovaquone-proguanil. However, mefloquine is not currently available on the South African market.
- **Children:** There is very limited RCT data in children.

PHC LEVEL ERC AND NEMLC RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: The PHC/Adult Hospital Level Committee suggests that doxycycline be used as malaria chemoprophylaxis in non-pregnant adults.

Rationale: Available evidence shows that doxycycline reduces parasitemia and clinical malaria due to *P falciparum.* Furthermore, mefloquine is currently unavailable in South Africa, and atovaquone-proguanil is unaffordable.

Level of Evidence: Low certainty evidence

Review indicator: Price reduction of atovaquone-proguanil, availability of mefloquine

NEMLC MEETING OF 24 JUNE 2021:

NEMLC Recommendation: The NEMLC accepted the recommendation of doxycycline as malaria chemoprophylaxis as proposed by the PHC/Adult Hospital Level Committee, but included children ≥8 years of age[a].

Recommended dosing:

- *Non-pregnant adults:* Doxycycline oral, 100 mg daily, taken from 2 days prior to entering endemic area until 4 weeks after exiting the endemic area.
- *Children ≥ 8 years of age:* Doxycycline oral, 2.2 mg/kg/dose daily, taken from 2 days prior to entering endemic area until 4 weeks after exiting the endemic area.

Note: Pregnant women and children <8 years of age should avoid travelling to endemic areas. However, if this cannot be avoided, self-provided malaria chemoprophylaxis should be considered (as recommended by the National Department of Health Malaria Treatment Guidelines)

Monitoring and evaluation considerations

Research priorities

a. SAMF, 2020 edition

BACKGROUND

The World Health Organization recommends chemoprophylaxis for migrant workers and travellers, travelling to endemic malaria areas at no cost to the individual.[1] The National Guidelines for the Prevention of Malaria, South Africa (2018) supports South Africa's target for malaria elimination by 2020 and recommends various preventative measures for malaria, including chemoprophylaxis.[2]

The burden of malaria in South Africa, as reported by the South African Malaria Elimination Committee differs from other African regions. Other African regions report malaria cases mostly amongst children and pregnant woman, whilst in South Africa more than 70% cases are in adult males primarily imported from other countries. Those affected are mainly mobile populations who are usually uninsured and unable to access chemoprophylaxis before travel to endemic areas. [3,4]

The National Department of Health's strategic priorities are to (1) advance elimination in areas like KwaZulu Natal sub-districts and (2) reduce morbidity and mortality in Gauteng, where studies showed a malaria case fatality rate of 4% (which exceeds the WHO target of ≤ 0.5%). Due to the high malaria notification rates in Gauteng (a non-malaria endemic province in South Africa) the Gauteng Provincial Department of Health piloted public sector travel clinics, with the provision of malaria chemoprophylaxis to 327 travellers in the 2019/2020 financial year. [3,4]

Local resistance to chloroquine and sulfadoxine-pyrimethamine is common and these agents are currently not recommended as monotherapy for malaria chemoprophylaxis.[2] The currently recommended agents are mefloquine, atovaquone-proguanil and doxycycline which are registered in South Africa. However, mefloquine has recently been withdrawn from the South African market.

Malaria chemoprophylaxis for travellers to malaria-endemic areas is currently not included in the Primary Healthcare Standard Treatment Guidelines and Essential Medicines List. The purpose of this review is to interrogate the evidence (dosing, efficacy, safety and tolerability) for malaria chemoprophylaxis (mefloquine, atovaquone-proguanil or doxycycline) for adults, specifically migrant workers traveling to and from endemic areas outside and within South Africa.

INTRODUCTION

Malaria chemoprophylaxis works by blocking the development or reproduction of the malaria parasite at various stages in its life cycle. Preventative options for the dominant species, *P. Falciparum*, outlined in the National Guidelines for the Prevention of Malaria, South Africa (2018) include atovaquone-proguanil, doxycycline, mefloquine.[5]

Atovaquone 250mg combined with 100 mg proguanil hydrochloride is a fixed dose combination started one to two days before travel to the endemic area. Unlike doxycycline and mefloquine which should be continued for 4 weeks post travel, the atovaquone-proguanil combination can be discontinued a week after leaving an endemic area because atovaquone hydrochloride's mechanism of action is against the early liver stages of *P. falciparum*. However, despite publication of a good side effect profile, there is limited evidence for the use of atovaquone in high-risk groups such as pregnant women, children, and long-term travellers.[5]

Doxycycline is a blood schizontocide. Since these forms of the parasite are only present later in the malarial lifecycle, doxycycline must be continued for at least 4 weeks post travel to the malaria area. Areas of concern include its gastrointestinal tolerance, its contraindication in pregnancy and the side effect of photosensitivity. Doxycycline for malaria use is taken as a single daily dose of 100mg, starting one to two days before entering the endemic area, continuing daily while in the endemic area and only stopping the daily dose 4 weeks after leaving the endemic area.[5]

Mefloquine, which also acts on the malarial blood schizonts, offers a once weekly dosing advantage which encourages adherence[6]. Mefloquine is started 1 week before travel and like doxycycline is taken until 4 weeks after return from the malaria area. The agent can be used for long term travellers, pregnant women, breastfeeding women, small children weighing >5 kg and is a popular choice due to the dosing convenience. The recommended adult dose for chemoprophylaxis is 250 mg weekly as a single dose.[5]

Adverse events associated with malaria chemoprophylaxis, particularly neuropsychiatric side effects may affect adherence rates.

To reach a recommendation for the PHC STGs and EML, a review of the efficacy and safety profile is required for malaria prophylaxis.

QUESTION: Which Malaria Prophylaxis regimen should be recommended for travellers to malaria endemic areas in and outside South Africa?

METHODS

Eligibility criteria for review

Population: Children & Adults at risk of malaria

Intervention: Antimalarial agent used as prophylaxis [atovaquone-proguanil, doxycycline & mefloquine]

Comparators: Placebo, or no treatment, or alternative antimalarial

Outcomes: Malaria incidence, deaths, deaths due to malaria, safety

Study designs: Systematic Reviews and RCTs

Two reviewers (JN, MR) searched two electronic databases (Cochrane library and PubMed) on 17th and 19 February 2021, including systematic reviews and meta-analyses of randomised controlled trials (RCTs). We excluded observational studies, case reports, case series and narrative reviews. Publications were restricted to those published in English. The search strategy is shown in Appendix 1. One reviewer screened records and extracted data (MR). Screening of records was done independently and in duplicate (JN, MR), with disagreement resolved through discussion. Excluded studies with the rationale for exclusion are summarised in Table 1; whilst relevant study data were extracted in a narrative table of results (MR, TL). JN and PN reviewed the overall report.

The quality of evidence was assessed independently using the AMSTAR 2 tool[7] for systematic reviews (MR, JN, PN, TL).

RESULTS

Results of search

A search resulted in a total of 62 articles (Pubmed (n=53) and the Cochrane Library (n=9)). After the removal of 20 duplicates, 42 articles were reviewed for eligibility by two reviewers (JN, MR). One systematic review was selected. Of the remaining 41 articles 29 studies were excluded due to studies not meeting PICO or an update of the study being available. Of the remaining 13 records, 10 RCTs were excluded because the studies were included in the systematic review. Bibliographies of excluded systematic reviews were checked to ensure that no RCTs were missed. One RCT was identified and included, while a further 2 studies were excluded. After discussions, one RCT from the systematic review was extracted and elaborated on in the review. Therefore, 4 studies (1 systematic review[8] and 3 RCTs[9, 10, 11]) were included in this review.

Studies were excluded if they did not meet the eligibility criteria or were systematic reviews that included duplicate RCTs already included in other reviews. Table 1 summarises the studies excluded from the review. Table 2 reports the main characteristics and outcomes reported in the included systematic reviews and RCTs.

Description of the included studies

One systematic review and 3 RCTs were included in this review. Two of the 3 RCTs were not included in the systematic review, whilst the RCT of doxycycline was extracted from the systematic review to provide more information on doxycycline as an antimalarial agent. The study populations in the included studies included pregnant woman, travellers from endemic areas (male and female) and male soldiers. RCT evidence for children is very limited and this

topic has been deferred to the Paediatric Hospital Level Committee for further review. A description of the included studies follows.

Tickell-Painter *et al*., 2017[8] conducted a systematic review of 20 RCTs (n=11,470), 35 cohort studies (n=198,493) and 4 large retrospective analyses (n=800,652) of health records in adults (including pregnant woman and children).

The systematic review was considered to be of high quality (see the Amstar2 assessment in appendix 2).

MEFLOQUINE VS PLACEBO

Efficacy: Mefloquine was highly efficacious in reducing clinical cases of malaria [17/1179 (1.4%) vs 153/729 (21.0%); NNT 6 (95% CI 5 to 7); RR 0.09 (95% CI 0.04 to 0.19); I^2=53%], *low certainty evidence* (see figure 1).

Overall, mefloquine also reduced cases of parasitaemia by 82% [18/183 (9.8%) vs 139/231(60.2%); NNT 2 (95% CI 1.7 to 2.3); RR 0.18, 95% CI 0.06 to 0.55; 3 RCTs; n=414; I^2=80%], *low certainty evidence.*

Mefloquine also substantially reduced the number of episodes of parasitaemia [22/262 (8.4%) vs 157/248 (63.3%); NNT 2 (95% CI 1.6 to 2.1); RR 0.05, 95% CI 0.00 to 5.25; 2 RCTs; n=510; I^2=91%], *low certainty evidence.*

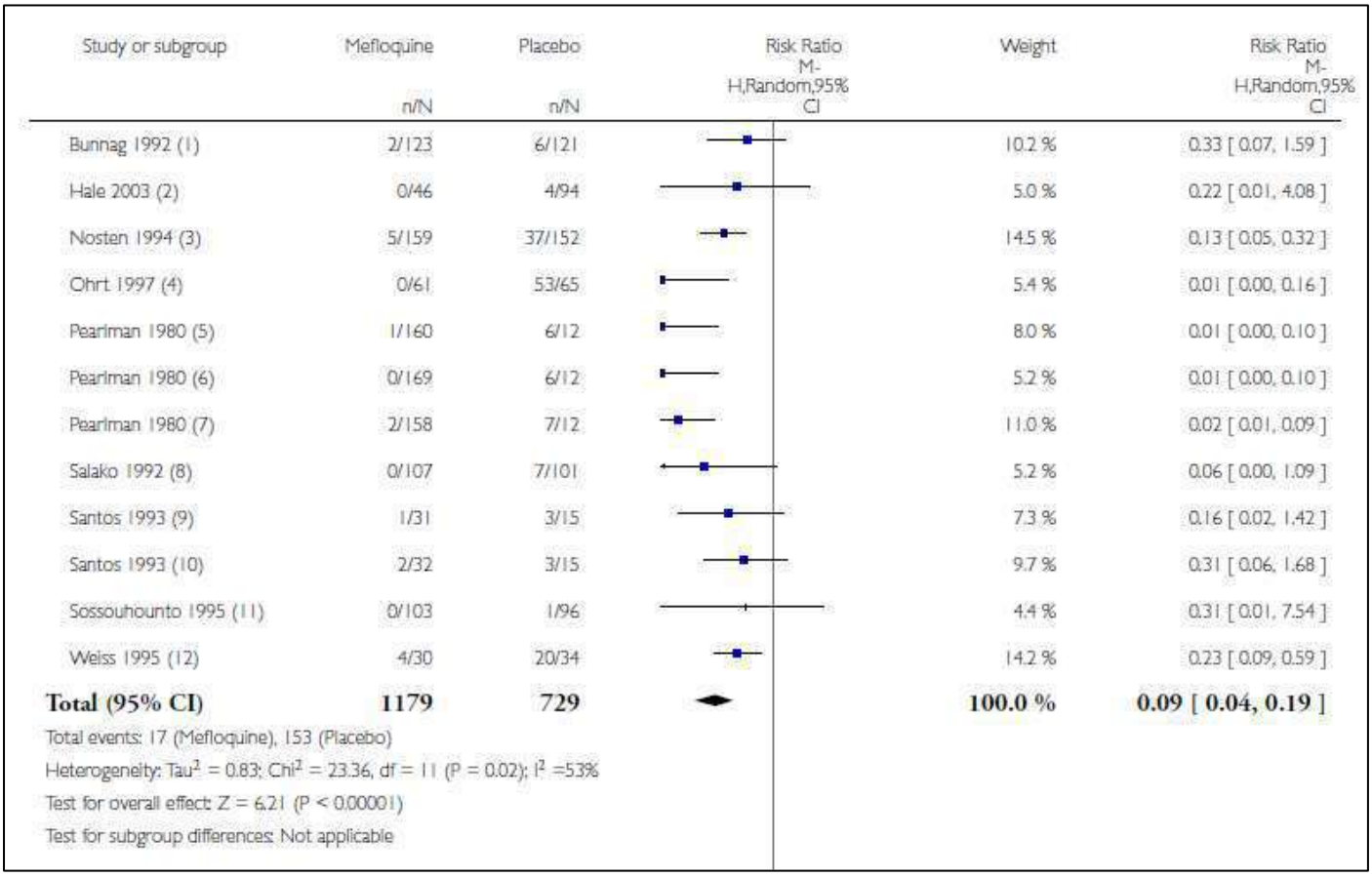

Figure 1: Forest plot of mefloquine vs placebo/non users for the outcome: clinical cases of malaria

Adverse events:

Seven serious adverse effects (n=5 psychological (depression) and n=2 neurological (dizziness)) was reported among 913 mefloquine users, compared to none in 254 travellers who did not use antimalarials (RR 3.08, 95% CI 0.39 to 24.11, 2 cohort studies, n=1167). NNH=130 (95%CI: 75.0 to 497.75 for the mefloquine group).

- Nausea: Mefloquine users were more likely to experience nausea than those who took placebo (RR 1.35, 95% CI 1.05 to 1.73; 2 trials, n=244).
- Vomiting, abdominal pain or diarrhoea: No difference between groups. One RCT in pregnant women reported on both upper and lower abdominal pain.
- Neurological symptoms: Mefloquine users were no more likely to experience headache (RR 0.84, 95% CI 0.71 to 0.99; 5 trials, n=791) or dizziness (RR 1.03, 95% CI 0.90 to 1.17; 3 trials, n=452). Psychological symptoms: None of the RCTs reported on prespecified psychological symptoms.

- Other: No difference between groups for visual impairment and vertigo in RCTs. Respiratory tract infection reached statistical significance between groups in a single trial with few events (RR 2.63, 95%CI 1.04 to 6.61; 1 trial, n=140).
- Pregnancy outcomes: No difference for spontaneous abortions (RR 0.48, 95% CI 0.04 to 5.22; n=311), still births (RR 2.63, 95%CI 0.86 to 8.08; n=311) or congenital malformations (RR 3.82, 95% CI 0.43 to 33.83; 311 pregnant women). However, the trial was significantly underpowered to evaluate these outcomes.

Discontinuation: Discontinuation due to adverse effects was low in both groups: 6/541 (1.1%) with mefloquine vs 4/583 (0.7%) with placebo (RR 1.64, 95% CI 0.55 to 4.88; 7 trials, n=1124).

MEFLOQUINE VS DOXYCYCLINE

Efficacy: Mefloquine shown to be comparable to doxycycline in preventing clinical malaria (4/378 vs 3/366 clinical cases; RR 1.35, 95% CI 0.35 to 5.1; 4 RCTs; n=744; I^2=3%), low certainty evidence. The RCT by Weiss et al (1995)[11], included in the analysis reported on episodes of parasitaemia in the semi-immune population, but there was no clear difference between the groups (RR 1.47, 95% CI 0.68 to 3.14; n=62). See figure 2, below.

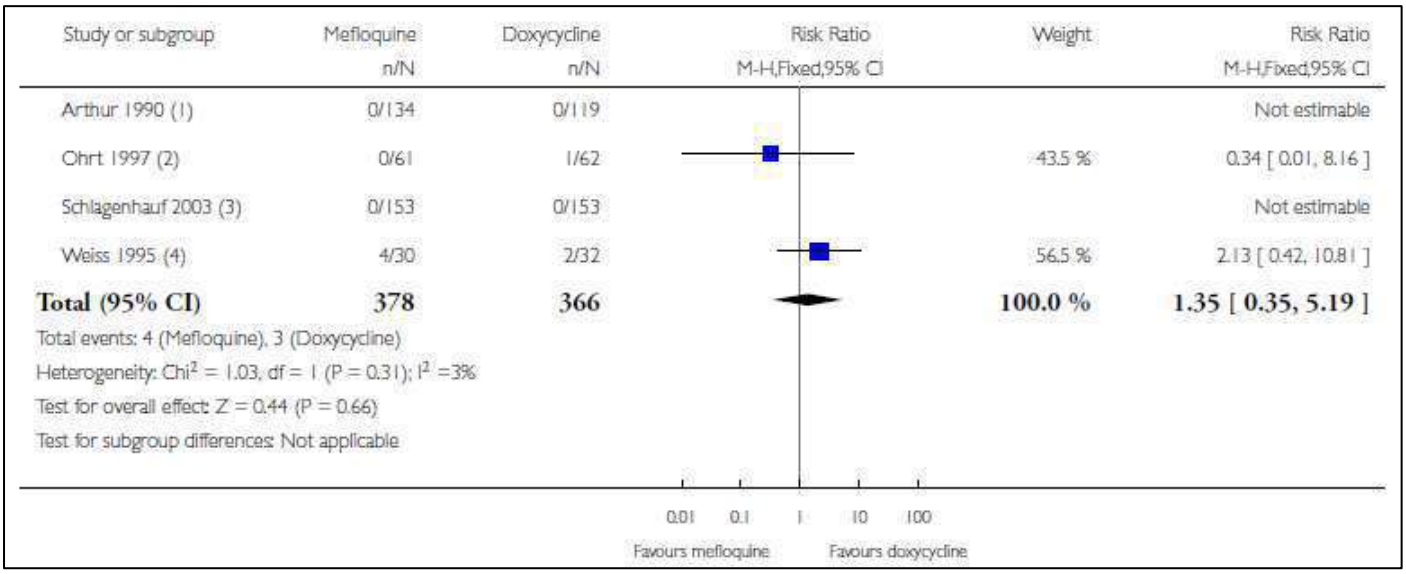

Figure 2: Forest plot of mefloquine vs doxycycline for the outcome: clinical cases of malaria.

Adverse events:
No difference was found in numbers of serious adverse effects with mefloquine and doxycycline (*low-certainty evidence*) or numbers of discontinuations due to adverse effects (RR 1.08, 95% CI 0.41 to 2.87; 4 RCTs, n=763; *low-certainty evidence*).

Safety data from 6 cohort studies in longer-term occupational travellers reporting on adverse effects, 1 RCT in military personnel and 1 cohort study in short-term travellers was analysed. Mefloquine users were reported to be more likely to report abnormal dreams (RR 10.49, 95% CI 3.79 to 29.10; 4 cohort studies, n= 2588 participants, *very low-certainty evidence*), insomnia (RR 4.14, 95% CI 1.19 to 14.44; 4 cohort studies, n= 3212, *very low-certainty evidence*), anxiety (RR 18.04, 95%CI 9.32 to 34.93; 3 cohort studies, n=2559 participants, *very low-certainty evidence*), and depressed mood (RR 11.43, 95% CI 5.21 to 25.07; 2 cohort studies, n=2445, *very low-certainty evidence*). However, the RCT in military personnel did not demonstrate a difference between groups in frequencies of abnormal dreams or insomnia.

Mefloquine users were also less likely to report gastrointestinal adverse effects compared to doxycycline: such as dyspepsia (RR 0.26, 95% CI 0.09 to 0.74; 5 cohort studies, n= 5104 participants, *low certainty evidence*), photosensitivity (RR 0.08, 95% CI 0.05 to 0.11; 2 cohort studies, n=1875 participants, *very low-certainty evidence*), vomiting (RR 0.18, 95% CI 0.12 to 0.27; 4 cohort studies, n=5071, *very low-certainty evidence*), and vaginal thrush (RR 0.10, 95% CI 0.06 to 0.16; 1 cohort study, n=1761, *very low-certainty evidence*).

Based on the available evidence, estimates of absolute effect for mefloquine versus doxycyline were reported as: 2% vs 2% for discontinuation, 12% vs 3% for insomnia, 31% vs 3% for abnormal dreams, 18% vs 1% for anxiety, 11% vs 1% for depressed mood, 4% vs 14% for dyspepsia, 2% vss 19% for photosensitivity, 1% vs 5% for vomiting, and 2% vs 16% for vaginal thrush.

MEFLOQUINE VS ATOVAQUONE-PROGUANIL

Efficacy: No clinical cases of malaria were recorded amongst 636 mefloquine users or 657 atovaquone-proguanil users (2 RCTs).

Adverse events: The mefloquine group was more likely to discontinue medication due to adverse effects vs atovaquone-proguanil (RR 2.86, 95% CI 1.53 to 5.31; 3 RCTs, n=1438, high certainty evidence) and there were few SAEs reported (15/2651 amongst mefloquine users and 0/940 amongst atovaquone-proguanil users).

Safety data from 1 RCT and 6 cohort studies were analysed. In the RCT with short-term travellers, mefloquine users were more likely to report abnormal dreams (RR 2.04, 95% CI 1.37 to 3.04, *moderate-certainty evidence*), insomnia (RR 4.42, 95% CI 2.56 to 7.64, *moderate-certainty evidence*), anxiety (RR 6.12, 95% CI 1.82 to 20.66, *moderate-certainty evidence*), and depressed mood during travel (RR 5.78, 95% CI 1.71 to 19.61, *moderate-certainty evidence*). The cohort studies in longer-term travellers were consistent with this finding but most had larger effect sizes. Mefloquine users were also more likely to report nausea (RR 2.72, 95% CI 1.52 to 4.86; n=976, *high-certainty evidence*) and dizziness (RR 3.99, 95% CI 2.08 to 7.64, *high-certainty evidence*).

Based on the available evidence, estimates of absolute effect sizes for mefloquine vs atovaquone-proguanil users were reported as 6% vs 2% for discontinuation of the drug, 13% vs 3% for insomnia, 14% vs 7% for abnormal dreams, 6% vs 1% for anxiety, and 6% vs 1% for depressed mood.

ATOVAQUONE-PROGUANIL VS PLACEBO

Two additional RCTs were reviewed, as they were not included in the systematic review:

- Soto *et al*., 2006[9] compared atovaquone/proguanil hydrochloride 250/100mg with placebo in a double-blind, RCT (n=180 male soldiers) in predominately *Plasmodium vivax* areas of Colombia, and
- Ling *et al*., 2002[10] conducted a randomized, double-blinded RCT (n=297) of migrants moving from non-endemic areas in Indonesia to endemic Papua about 26 months prior to the start of the study. Atovaquone/proguanil hydrochloride 250/100mg (n=148) was compared to placebo (n=149) per day for 20 weeks. Only 85/148 study participants from the atovaquone-proguanil and 124/149 from the placebo group, completed the study.

Efficacy:

- Soto *et al*., 2006[9] showed that of atovaquone-proguanil's protective efficacy for *Plasmodium falciparum* was 100%. No cases (0/120) of *Plasmodium falciparum* infection was reported with use of atovaquone-proguanil, whilst 2 case (2/60) occurred in the control arm.
- In the study by Ling *et al*., 2002[10] protective efficacy of atovaquone/proguanil against *Plasmodium falciparum* was shown to be 96% (95% CI, 72 to 99%) when compared to placebo – 1/150 cases reported in the atovaquone/proguanil group and 23/149 were reported in the placebo group. Malaria cases due to co-infection with both *Plasmodium vivax* and *Plasmodium falciparum* were also reported. The overall protective efficacy of atovaquone/proguanil against *Plasmodium falciparum* and *Plasmodium vivax* infection was reported to be 93% (95% CI, 77%–98%). The study was double-blinded and an ITT analysis was used; however, as attrition rate was >20%, being much higher in the atovaquone/proguanil than the placebo group, the evidence was considered of very low quality.

Adverse Events:

- *Serious Adverse Events:* Soto *et al*., 2006[9] reported no serious adverse. Ling *et al*., 2002[10] reported that four atovaquone-proguanil subjects had severe adverse effects (3 abdominal pain and 1 skin rash). However, the skin rash was considered potentially viral as 2 other non-study subjects in the same village had a similar occurrence.

- *Discontinuation of antimalarial*: Soto *et al*., 2006[9] had no subject discontinuing study medication because of adverse events. In the study by Ling *et al*., 2002[10],4 participants withdrew from the study due to adverse events (one in the atovaquone-proguanil group and 3 in the control group).
- *Common adverse events:* Soto *et al*., 2006[9] reported the following adverse events for atovaquone-proguanil vs placebo as*:* tinea infection (18% vs 28%), parasitic gastrointestinal infection (7% vs 5%), headache (7% vs 3%) and fever (5% vs 0%). In Ling *et al*., 2002[10], stomatitis and back pain appeared more frequently amongst atovaquone-proguanil recipients and abdominal pain and malaise occurred more frequently in the placebo group).

DOXYCYCLINE VS CONTROL

Weiss et al.[11] conducted a study on Kenyan children (9-14 years of age), n=169. It included several arms in two groups (weekly and daily prophylaxis groups). Following curative treatment, participants in the daily prophylaxis groups were randomised to doxycycline vs primaquine vs proguanil + weekly chloroquine vs weekly mefloquine + vitamin vs vitamin alone. Each were given for 11 weeks, with a 3-week subsequent follow-up period. For the purposes of comparison, the multivitamin tablet can be considered a placebo. Outcomes measured were parasitaemia, clinical malaria and side effects. Compared to vitamins (placebo), doxycycline was 84% effective (95% CI 66-92%) at preventing parasitaemia; NNT 4 95% CI 3 to 10), and 91% effective (95% CI 61 to 98%) at preventing clinical malaria; NNT 16 (95% CI 7 to 47). No significant differences in side effects between the vitamin group and the group receiving doxycycline.

LOCAL RESISTANCE PATTERNS

The South African Malaria Elimination Committee advised that local susceptibility is not collected for malaria. However, there is some concerning evidence for artemesinin resistance in some parts of Africa. Regarding prophylaxis, there is no indication that atovaquone/proguanil or doxycycline or mefloquine are facing resistance challenges. However, previous prophylaxis regimens (chloroquine and choroquine-proguanil) are no longer acceptable, based on resistance.[12]

PREGNANCY-RELATED OUTCOMES

All guidelines recommend that pregnant women should avoid not travel to malaria-endemic areas, however if this is unavoidable, mefloquine is the preferred option. Mefloquine is considered to be safe within the second and third trimesters of pregnancy and guidelines are increasingly recommending use in the first trimester. Mefloquine is also suitable for children who weigh more than 5 kg and breastfeeding mothers. Doxycycline has restrictions on its use during pregnancy due to effects on skeletal development found in animal studies. For atovaquone-proguanil, there is a paucity of safety data in pregnancy.

For serious pregnancy-related outcomes, Tickell-Painter *et al*. 2017[8] report on the findings from Nosten *et al*.[13] that reported 4 congenital malformations in the mefloquine study arm: 1 case of limb dysplasia, 2 cases of ventricular septal defect, and 1 case of amniotic bands (1 case) and one case of anencephaly in the placebo group. However, all were considered to be unrelated to mefloquine prophylaxis.

CONCLUSION

Available evidence shows that atovaquone-proguanil, doxycycline or mefloquine has comparable protective efficacy against *Plasmodium falciparum,* when compared to placebo. Discontinuation of therapy due to associated adverse events was more likely with mefloquine and doxycycline and less likely with atovaquone-proguanil. Mefloquine is associated with more neurological disorders (abnormal dreams, insomnia, anxiety and depressed mood), whilst doxycycline was reported to more likely be associated with dyspepsia, photosensitivity, vomiting, and vaginal thrush. Mefloquine is considered the safest option in pregnancy, but is currently not available in South Africa. Factors for consideration to determine the choice of antimalarial agent includes resistance patterns of the affected malaria-endemic area(s), associated adverse events and pill burden, that would impact patient adherence, and cost.

Reviewer(s): Ms T Leong, Dr R Reddy, Dr J Nel, Prof P Nyasulu.

Declaration of interests: TL (Essential Drugs Programme, National Department of Health), MR (Better Health Programme, South Africa), JN (Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand) and PN (Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University) have no conflicts to declare pertaining to this review.

Table 2: Excluded studies

No	Reference	Reason for Exclusion
1	González R et al. Mefloquine for preventing malaria in pregnant women. Cochrane Database Syst Rev. 2018 Mar 21;3(3):CD011444. Doi: 10.1002/14651858.CD011444.pub2. Update in: Cochrane Database Syst Rev. 2018 Nov 14;11:CD011444.	Duplicate /Update available
2	Rodrigo C, et al . Tafenoquine for primary and terminal prophylaxis of malaria in apparently healthy people: a systematic review. Trans R Soc Trop Med Hyg. 2019 Oct 11;113(10):579-586. Doi: 10.1093/trstmh/trz052.	Does Not Meet PICO
3	Tickell-Painter M, et al. Deaths and parasuicides associated with mefloquine chemoprophylaxis: A systematic review. Travel Med Infect Dis. 2017 Nov-Dec;20:5-14. Doi: 10.1016/j.tmaid.2017.10.011.	Case Reports and only 1 RCT included in the Cochrane Review
4	González et al. Mefloquine safety and tolerability in pregnancy: a systematic literature review. Malar J. 2014 Feb 28;13:75. Doi: 10.1186/1475-2875-13-75.	Of the relevant RCTs, these were included in Cochrane Review
5	Croft AM, Garner P. WITHDRAWN: Mefloquine for preventing malaria in non- immune adult travellers. Cochrane Database Syst Rev. 2008 Jan 23;2000(1):CD000138. Doi: 10.1002/14651858.CD000138.pub2. PMID: 18253969; PMCID: PMC6532714.	Withdrawn
6	Croft AM et al . Mefloquine for preventing malaria in non-immune adult travellers. Cochrane Database Syst Rev. 2000;(4):CD000138. Doi: 10.1002/14651858.CD000138. Update in: Cochrane Database Syst Rev. 2008;(1):CD000138.	Review Updated
7	Croft A et al . Mefloquine to prevent malaria: a systematic review of trials. BMJ. 1997 Nov 29;315(7120):1412-6. Doi: 10.1136/bmj.315.7120.1412. PMID: 9418088; PMCID: PMC2127902.	Articles included in Cochrane Review
8	Muanda FT et al. Antimalarial drugs for preventing malaria during pregnancy and the risk of low birth weight: a systematic review and meta-analysis of randomized and quasi-randomized trials. BMC Med. 2015 Aug 14;13:193. Doi:10.1186/s12916-015-0429-x.	Of 25 RCTS – 24 appear in one of the Cochrane Reviews. 1 Article was not relevant
9	Croft AM. Malaria: prevention in travellers. BMJ Clin Evid. 2010 Jul 12;2010:0903. PMID: 21418669; PMCID: PMC3217660.	Excluded - Duplicate RCTs included in this review.
10	Zhou LJ et al. Risk of drug resistance in *Plasmodium falciparum* malaria therapy-a systematic review and meta-analysis. Parasitol Res. 2017 Feb;116(2):781-788. Doi: 10.1007/s00436-016-5353-2.	Treatment / Does Not Meet PICO
11	Bitta MA et al . Antimalarial drugs and the prevalence of mental and neurological manifestations: A systematic review and meta-analysis. Wellcome Open Res. 2017 Jun 2;2:13. Doi: 10.12688/wellcomeopenres.10658.2.	Of the 50 articles included, some were included in the Cochrane Review, others were not applicable
12	Jacquerioz FA et al. Drugs for preventing malaria in travellers. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006491. Doi: 10.1002/14651858.CD006491.pub2. Update in: Cochrane Database Syst Rev. 2015;10:CD006491.	Update Available
13	Croft AM. Malaria: prevention in travellers. BMJ Clin Evid. 2007 Nov 29;2007:0903.	Duplicate /Update Available
14	Griffith KS et al . Treatment of malaria in the United States: a systematic review. JAMA. 2007 May 23;297(20):2264-77. Doi: 10.1001/jama.297.20.2264.	Malaria treatment
15	Frimpong A et al. Safety and effectiveness of antimalarial therapy in sickle cell disease: a systematic review and network meta-analysis. BMC Infect Dis. 2018 Dec 12;18(1):650. Doi: 10.1186/s12879-018-3556-0. PMID: 30541465; PMCID: PMC6292161.	Does Not Meet PICO requirements
16	Graves PM et al. Primaquine or other 8-aminoquinolines for reducing *Plasmodium falciparum* transmission. Cochrane Database Syst Rev. 2018 Feb 2;2(2):CD008152. Doi: 10.1002/14651858.CD008152.pub5. PMID: 29393511; PMCID: PMC5815493.	Does Not Meet PICO requirements
17	Kolifarhood G et al. Prophylactic efficacy of primaquine for preventing *Plasmodium falciparum* and *Plasmodium vivax* parasitaemia in travelers: A meta-analysis and systematic review. Travel Med Infect Dis. 2017 May-Jun;17:5-18. Doi: 10.1016/j.tmaid.2017.04.005. Epub 2017 Apr 24. PMID: 28450185.	Does Not Meet PICO requirements
18	Graves PM et al. Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission. Cochrane Database Syst Rev. 2015 Feb 19;(2):CD008152. Doi: 10.1002/14651858.CD008152.pub4. Update in: Cochrane Database Syst Rev. 2018 Feb 02;2:CD008152. PMID: 25693791; PMCID: PMC4455224.	Does Not Meet PICO requirements
19	Graves PM et al. Primaquine for reducing *Plasmodium falciparum* transmission. Cochrane Database Syst Rev. 2012 Sep 12;(9):CD008152. Doi: 10.1002/14651858.CD008152.pub2. Update in: Cochrane Database Syst Rev. 2014;(6):CD008152. PMID: 22972117.	Does Not Meet PICO requirements
20	Graves et al. Primaquine or other 8-aminoquinoline for reducing *P. falciparum* transmission. Cochrane Database Syst Rev. 2014 Jun 30;(6):CD008152. Doi: 10.1002/14651858.CD008152.pub3. Update in: Cochrane Database Syst Rev. 2015;(2):CD008152. PMID: 24979199; PMCID: PMC4456193.	Does Not Meet PICO requirements
21	Jacquerioz FA et al. WITHDRAWN: Drugs for preventing malaria in travellers. Cochrane Database Syst Rev. 2015 Oct 5;(10):CD006491. Doi: 10.1002/14651858.CD006491.pub3. Update in: Cochrane Database Syst Rev. 2017 Oct 30;10 :CD006491. PMID: 26436859.	Paper Withdrawn
22	Hossain MS et al. The risk of Plasmodium vivax parasitaemia after *P. falciparum* malaria: An individual patient data meta- analysis from the WorldWide Antimalarial Resistance Network. PloS Med. 2020 Nov 19;17(11):e1003393. Doi: 10.1371/journal.pmed.1003393.	Does Not Meet PICO requirements
23	Garner P et al. A review of randomized controlled trials of routine antimalarial drug prophylaxis during pregnancy in endemic malarious areas. Bull World Health Organ. 1994;72(1):89-99.	Relevant papers included in the Cochrane Review
24	Goetze S et al. Phototoxicity of Doxycycline: A Systematic Review on Clinical Manifestations, Frequency, Cofactors, and Prevention. Skin Pharmacol Physiol. 2017;30(2):76-80.	Does Not Meet PICO requirements

No	Reference	Reason for Exclusion
25	Andrejko KL, et al. The safety of atovaquone-proguanil for the prevention and treatment of malariain pregnancy: A systematic review. Travel Med Infect Dis. 2019 Jan-Feb;27:20-26.	Not Relevant to Prophylaxis/ Does Not Meet PICO requirements
26	Savelkoel J et al. Abbreviated atovaquone-proguanil prophylaxis regimens in travellers after leaving malaria-endemic areas: A systematic review. Travel Med Infect Dis. 2018 Jan Feb;21:3-20.	Does not Meet PICO requirements
27	Staines HM et al. Clinical implications of Plasmodium resistance to atovaquone/proguanil: a systematic review and meta-analysis. J Antimicrob Chemother. 2018 Mar 1;73(3):581-595.	Treatment/ Does Not Meet PICO requirements
28	Nakato H et al. A systematic review and meta-analysis of the effectiveness and safety of atovaquone proguanil (Malarone) for chemoprophylaxis against malaria. J Antimicrob Chemother. 2007 Nov;60(5):929-36.	3 RCTs from this review that were not included in the Cochrane Reviews
29	Garner P et al. Drugs for preventing malaria in pregnant women. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD000169.	Does Not Meet PICO requirements
30	Leoni S et al. The hyper-reactive malarial splenomegaly: a systematic review of the literature. Malar J. 2015 Apr 29;14:185.	Does Not Meet PICO requirements
31	Raquel González et al Mefloquine for preventing malaria in pregnant women. Cochrane Database Syst Rev. 2018 Mar 21;3(3):CD011444	Does Not Meet PICO requirements
32	Tickell-Painter M et al Mefloquine for preventing malaria during travel to endemic areas. Cochrane Database Syst Rev. 2017 Oct 30;10(10):CD006491.	Duplicate
33	Piero L Olliaro et al. Amodiaquine for treating malaria. Cochrane Database Syst Rev. 2000;(2):CD000016.	Does Not Meet PICO requirements
34	Oniyangi O et al. Malaria chemoprophylaxis in sickle cell disease. Cochrane Database Syst Rev. 2019 Nov 4;2019(11)	Does Not Meet PICO requirements
35	Gogtay N et al. Artemisinin-based combination therapy for treating uncomplicated Plasmodium vivax malaria. Cochrane Database Syst Rev. 2013 Oct 25;2013(10):CD008492.	Does Not Meet PICO requirements
36	Mathanga DP et al.Intermittent preventive treatment regimens for malaria in HIV-positive pregnant women. Cochrane Database Syst Rev. 2011 Oct 5;2011(10):CD006689.	Does Not Meet PICO requirements
37	Radeva-Petrova D et al Drugs for preventing malaria in pregnant women in endemic areas: any drug regimen versus placebo or no treatment. Cochrane Database Syst Rev. 2014 Oct 10;2014(10):CD000169.	Duplicate
38	Tomas Pantoja et al. Implementation strategies for health systems in low-income countries: an overview of systematic reviews.. Cochrane Database Syst Rev. 2017 Sep 12;9(9):CD011086.	Does Not Meet PICO requirements
39	Catherine Lees et al. Neonatal screening for sickle cell disease Intervention. Cochrane Database Syst Rev. 2000;(2):CD001913.	Does Not Meet PICO
40	Radeva-Petrova D et al. Drugs for preventing malaria in pregnant women in endemic areas: any drug regimen versus placebo or no treatment. Cochrane Database Syst Rev. 2014 Oct 10;2014(10):CD000169.	Only 1 paper relevant to PICO and was already included in Tickell-Painter Cochrane Review
41	Raquel González et al Mefloquine for preventing malaria in pregnant women. Cochrane Database Syst Rev. 2018 Mar 21;3(3):CD011444	Duplicate
42	Høgh B, et al - Malarone International Study Team. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travellers: a randomised, double-blind study. Malarone International Study Team. Lancet. 2000 Dec 2;356(9245):1888-94.	Does Not Meet PICO requirements

RCT = Randomized Control Trial

Table 2: Characteristics of included studies

1) SYSTEMATIC REVIEW:

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
Tickell-Painter *et al.*, 2017[8]	Systematic Review: 20 RCTs, 35 cohort studies 4 large retrospective analyses of health records	Adults & children, including pregnant women. RCTs (n=11,470) Cohort studies (n=198,493) Retrospective Analyses (n=800,652) 9 RCTs excluded participants with a psychiatric history. 25 cohort studies choice of antimalarial based on medical history & personal preference	Mefloquine,250 mg once weekly in adults & equivalent dosing for children, vs placebo/ no intervention or alternative malaria chemoprophylaxis	**Efficacy:** Clinical cases of malaria **Safety:** • Adverse effects • Discontinuations due to adverse effects. • Adherence • Pregnancy-related outcomes: - adverse pregnancy outcomes - spontaneous abortions, stillbirths, congenital malformations.	**Efficacy:** <u>Mefloquine vs placebo:</u> • Developing malaria episode: o in the control arm varied from 1% to 82% (median 22%) & o 0% to 13% in the mefloquine group (median 1%). • Developing parasiteamia o 18/189 vs 139/231; NNT 11 (95% CI 8 to 19) <u>Mefloquine vs atovaquone-proguanil</u> o No clinical cases of malaria were recorded (2 RCTs, 636 mefloquine users; 657 atovaquone-proguanil users). **Doxycycline vs Mefloquine:** Similar numbers of participants were infected in both arms (3/366 doxycycline users vs 4 / 378 mefloquine users: RR 1.35, 95% CI 0.35 to 5.19; 4 trials, 744 participants) **<u>Safety:</u>** ***Mefloquine vs atovaquone-proguanil*** • Mefloquine grp more likely to: o discontinue medication due to AEs vs atovaquone-proguanil (RR 2.86, 95% CI 1.53 to 5.31; 3 RCTs, 1438 participants; NNT17 (95% CI 10 to 75) ***high-certainty evidence***). ▪ 15/2651 travellers) and 0 with atovaquone-proguanil (940 travellers). o more likely to report: ▪ abnormal dreams (RR 2.04, 95% CI 1.37 to 3.04, NNT 8 (95% CI 5 to 14) (***moderate-certainty evidence***), ▪ insomnia (RR 4.42, 95% CI 2.56 to 7.64, NNT 8 (95% CI 6 to 16) (***moderate-certainty evidence***), ▪ anxiety (RR 6.12, 95% CI 1.82 to 20.66, NNT 17 (95% CI 10 to 75) ***moderate-certainty evidence***), & ▪ depressed mood during travel (RR 5.78, 95% CI 1.71 to 19.61, NNT 17 (95% CI 10 to 75) ***moderate-certainty evidence***).	Systematic review of RCTs to determine efficacy and safety of various antimalarial agents. Observational studies were included in the safety review. Assessed as a high quality systematic review – see appendix 2 for the AMSTAR2 assessment. Included studies, though, were of low to very low quality.

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
					▪ nausea NNT 13 (95%CI 8 to 38) (**high-certainty evidence**) ▪ dizziness NNT 13 (95% CI 8 to 13) (***high-certainty evidence***). • **Absolute effect sizes: Mefloquine vs atovaquone-proguanil:** o 6% vs 2% - drug discontinuation o 13% vs 3% for insomnia o 14% vs 7% for abnormal dreams o 6% vs 1% for anxiety & o 6% vs 1% for depressed mood ***Doxycycline vs Mefloquine (Mefloquine RR reported)*** • No difference in serious adverse effects (***low-certainty evidence***) • No difference in discontinuations due to AEs (RR 1.08, 95% CI 0.41 to 2.87; 4 RCTs, 763 participants; ***low-certainty evidence***). • Doxycycline - less likely to report. Mefloquine RR reported o abnormal dreams (RR 10.49, 95% CI 3.79 to 29.10; 4 cohort studies, n=2588, ***very low-certainty evidence***), o insomnia (RR 4.14, 95% CI 1.19 to 14.44; 4 cohort studies, n=3212, ***very low-certainty evidence***), o anxiety (RR 18.04, 95% CI 9.32 to 34.93; 3 cohort studies, n=2559 ***very low-certainty evidence***), & o depressed mood (RR 11.43, 95% CI 5.21 to 25.07; 2 cohort studies, n=2445, ***very low-certainty evidence***). • Doxycycline more likely to report. Mefloquine RR reported o dyspepsia (RR 0.26, 95% CI 0.09 to 0.74; 5 cohort studies, n=5104, ***low certainty evidence***), o photosensitivity (RR 0.08, 95% CI 0.05 to 0.11; 2 cohort studies, n=1875, ***very low-certainty evidence***), o vomiting (RR 0.18, 95% CI 0.12 to 0.27; 4 cohort studies, n=5071) & o vaginal thrush (RR 0.10, 95% CI 0.06 to 0.16; 1 cohort study, n=1761, ***very low-certainty evidence***). • Based on the available evidence - **best estimates of absolute effect** - doxycycline vs mefloquine: o 2% vs 2% for discontinuation, o 3% vs 12% vs for insomnia,	

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
					○ 3% vs 31% for abnormal dreams, ○ 1% vs 18% for anxiety, ○ 1% vs 11% for depressed mood, ○ 14% vs 4% for dyspepsia, ○ 19% vs 2% for photosensitivity, ○ 5% vs 1% for vomiting, & ○ 16% vs 2% for vaginal thrush	

2) RANDOMISED CONTROLLED STUDIES:

• **ATOVAQUONE/PROGUANIL VS PLACEBO**						
Citation	**Study design**	**Population (n)**	**Treatment**	**Outcomes**	**Effect sizes**	**Comments**
Soto *et al*, 2006[9]	Phase IV, randomized, double blind, placebo-controlled single center trial	Colombia Non-immune Colombian soldiers, male, average age 19 years (17 to 27 years) Average weight 63 kg (48-81kg) 75% Hispanic & 25% black N=180 (120 atovaquone proguanil and 60 placebo)	250mg atovaquone + 100mg proguanil vs placebo One tablet daily with breakfast, from 1 day before entering the malaria endemic areas through 10–16 weeks of residence in the area and for 7 days after leaving the endemic areas Plasma sample was collected between weeks 5 and 7 and weeks 10 and 12, and if malaria exhibited, for determination drug concentrations	• Parasitemia Proportion who failed prophylaxis = number of subjects who failed/number of subjects treated Protective efficacy = 1– (proportion of atovaquone-proguanil failures/ proportion of placebo failures)	• n=24 unevaluable due to compliance issues, including n=1 atovaquone-proguanil subject (no detectable drug levels) who became infected -*P. vivax.* • 0/ 97 (100%) evaluable subjects who received atovaquone-proguanil parasitemic • 11/ 47 (23.4%) evaluable placebo subjects became infected with *P. vivax* and 2/47 (4.3%) infected with *Plasmodium falciparum*. • Protective efficacy of atovaquone-proguanil for all malaria and for *P. vivax* malaria was 100% (LL 95% CI =63%) and 100% (LL 95% CI = 58%), respectively (NNT 4, 95% CI 3 to 7) - and was 96% if the one case with undetectable blood levels was included. **<u>Adverse Events (AEs):</u>** • *Serious Adverse Events:* No SAEs reported. • *Discontinuation of antimalarial*: No subject discontinuing study medication because of adverse events. • *Common adverse events:* For atovaquone-proguanil vs placebo: tinea infection (18% vs 28%), parasitic gastrointestinal infection (7% vs 5%), headache (7% vs 3%) and fever (5% vs 0%).	Atovaquone-proguanil showed high protective efficacy compared to placebo. Small double-blinded RCT of very low certainty of evidence, with a very high attrition rate, restricted to male soldiers only.

Ling *et al*., 2002[10]	Randomized, double-blinded study	Individuals from non-endemicity (3 villages) in Indonesia who migrated to Papua (where malaria is endemic) ≤26 months before the study period
		
		N=297
		
		Aged 12–65 years and weighed 40 kg.
			3 distinct phases: (1) 17-day period of radical cure treatment, 20 weeks of prophylaxis, and 4 weeks of postprophylaxis follow up. Consisted of 1000mg of atovaquone and 400mg of proguanil hydrochloride (4 tablets, containing 250 mg of atovaquone and 100 mg of proguanil hydrochloride per tablet) given once daily with food for 3 days, followed by 2 primaquine phosphate tablets (15 mg primaquine per tablet) once daily for 14 days.
			
			After radical cure regimen, subjects randomized in 3:1 ratio to continue/ stop
			
			Subjects randomized to continue further randomized in a 1:1 ratio to receive 1 atovaquone-proguanil tablet or 1 placebo tablet daily for 20 weeks.
				Primary efficacy end point was the first occurrence of slide-proven *P. vivax* parasitemia.
				
				Secondary efficacy end point was first occurrence of slide proven *P. vivax* or *P. falciparum* parasitemia.
				
				% of efficacy was calculated as 100 x [1-(incidence density of malaria in atovaquone-proguanil recipients/incidence density of malaria in placebo recipients)].
				
				Adverse Events
					<u>Infection after the radical cure regimen:</u>
					• Malaria diagnosed in 40 subjects during the prophylaxis phase
					  ○ Parasitemia in 37 subjects in the placebo group
					  ▪ 14 cases due to *P. vivax* alone,
					  ▪ 21 due to *P. falciparum* alone, &
					  ▪ 2 due to *P. vivax–P. falciparum*
					  ○ Parasitemia in 3 subjects in atovaquone-proguanil group
					  ▪ 2 cases due to *P. vivax* alone &
					  ▪ 1 case due to *P. vivax–P. falciparum*.
					
					• The protective efficacy of atovaquone/proguanil:
					  ○ 84% (95% CI, 45%–95%) for *P. vivax,*
					  ○ 96% (95% CI, 71%–99%) for P. *falciparum, &*
					  ○ 93% (95% CI, 77%–98%) overall
					
					<u>During 4 weeks follow -up</u>
					• Parasitemia in:
					  ○ 5 subjects in the placebo group
					  ▪ n=3 *P. falciparum* &
					  ▪ n=2 *P. vivax* &
					  ○ 7 subjects in the atovaquone-proguanil group
					  ▪ n=2 *P. falciparum &*
					  ▪ *n*=5 *P vivax*
					
					<u>Adverse Events</u>
					• *Serious Adverse Events:* 4 SAEs - 3 abdominal pain and 1 skin rash (no causal effect with the skin rash SAE).
					• *Discontinuation of antimalarial*: 4 participants withdrew from the study due to adverse events (one in the atovaquone-proguanil group and 3 in the control group).
					• *Common adverse effects:* stomatitis and back pain appeared more frequently amongst atovaquone-proguanil recipients and abdominal pain and malaise occurred more frequently in the placebo group.)
						Atovaquone-proguanil showed high protective efficacy compared to placebo.
						
						Small double-blinded RCT, data analysed using ITT analysis.
						
						Very low certainty of evidence, with a very high attrition rate (that was not comparable between study gps).

<table>
<tr><th colspan="7">• DOXYCYCLINE VS PLACEBO</th></tr>
<tr><th>Citation</th><th>Study design</th><th>Population (n)</th><th>Treatment</th><th>Outcomes</th><th>Effect sizes</th><th>Comments</th></tr>
<tr>
<td>Weiss et al. 1995[11]</td>
<td>Randomised trial, slide readers and field workers were blinded.</td>
<td>Students from several villages in Saradidi Rural Health Program catchment area in Kenya. Ages 9-14.

N = 169</td>
<td>Curative treatment initially. Then (a) multivitamin tablet vs quinine on Mon, Wed, Fri for 12 weeks (“intermittent study”). Or (b) daily multivitamin vs daily doxycycline vs daily primaquine vs weekly mefloquine + daily multivitamin vs daily proguanil + weekly chloroquine (“daily study”) for 11 weeks.</td>
<td>Parasitaemia prevention efficacy

Clinical malaria prevention efficacy.</td>
<td>Parasitaemia prevention:
<table>
<tr><th>Regimen</th><th>Efficacy (95% CI)</th></tr>
<tr><td>Vitamin (n=34)</td><td>N/A</td></tr>
<tr><td>Primaquine (n=32)</td><td>85% (68-93%)</td></tr>
<tr><td>Doxycycline (n=32)</td><td>84% (66-92%); NNT 4 (3-10)</td></tr>
<tr><td>Mefloquine (n=30)</td><td>77% (55-88%)</td></tr>
<tr><td>Chloroquine + proguanil (n=37)</td><td>54% (25-72%)</td></tr>
</table>
Clinical malaria prevention
<table>
<tr><th>Regimen</th><th>Efficacy (95% CI)</th></tr>
<tr><td>Vitamin (n=34)</td><td>N/A</td></tr>
<tr><td>Primaquine (n=32)</td><td>83% (50-94%)</td></tr>
<tr><td>Doxycycline (n=32)</td><td>91% (61-98%); NNT 16 (7-17)</td></tr>
<tr><td>Mefloquine (n=30)</td><td>81% (44-93%)</td></tr>
<tr><td>Chloroquine + proguanil (n=37)</td><td>72% (35-88%)</td></tr>
</table>
Adverse events:
Mean number of symptoms per subject (doxycycline vs placebo)
• Headache 6.1 vs 7.0
• Fever 5.8 vs 5.3
• Diarrhea: 1 vs 1.2
• Stomach Pains: 8.3 vs 6.8
• Nausea: 4.9 vs 3.3</td>
<td>RCT was included in the systematic review by Tickell-Painter et al., 2017.

Small single-blinded RCT, comparing various antimalarials to control.

Random allocation of intervention/control, but allocation was likely not concealed.

Clinical malaria possibly over diagnosed (high pressure of malaria infection and symptoms may have been due to other diseases).

Potential participants with G6PD excluded.

Low certainty evidence as underpowered, single-blinded with possible selection and performance bias.</td>
</tr>
</table>

Appendix 1: Search strategy

Cochrane library *Search:* malaria prophylaxis in Cochrane Reviews **Records retrieved: 9 (3 Duplicates, 6 did not meet PICO)**
PUBMED *Search:* ("*plasmodium falciparum*"[All Fields]) AND ("primaquine"[All Fields]) **Filters:** Meta-Analysis, Systematic Review **Records retrieved: 52 (17 were duplicates, 35 did not meet PICO/incorrect study design/ update or duplicate or poor-quality design)**

Appendix 2: AMSTAR2 Assessment

Evaluating the methodological quality of the Tickell-Painter *et al.* (2017)[8] systematic review and meta-analysis using the AMSTAR 2 tool (Shea 2017[7]):

AMSTAR Assessments	
1. Research questions and inclusion criteria for the review included the components of PICO?	Yes
2. Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3. Review authors explained selection of the study designs for inclusion in the review?	Yes
4. Review authors used a comprehensive literature search strategy?	Yes
5. Review authors perform study selection and data extraction in duplicate?	Yes
6. Review authors provided a list of excluded studies and justify the exclusions?	Yes
7. Review authors described the included studies in adequate detail?	Yes
8. Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
9. Review authors reported on the sources of funding for the studies included in the review?	Yes
10. For meta-analyses, review authors used appropriate methods for statistical combination of results? (Random- vs fixed-effects)	n/a
11. For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis?	n/a
12. Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review?	Yes
13. Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
14. For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review?	No
15. Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

*Study authors explain that they were unable to assess publication bias using funnel plots due to high study heterogeneity.

Critical domains (2, 4, 7, 9)

Rating overall confidence in the results of the review

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

OVERALL ASSESMENT: High quality

Appendix 3: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Uncertain ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Systematic review by Tickell-Painter *et al.,* 2017[8], reviewed RCTs of low certainty evidence to determine the protective efficacy of antimalarial agents: mefloquine, atovaquone-proguanil and doxycycline.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☒ Moderate ☐ Small ☐ None ☐	Systematic review by Tickell-Painter *et al.,* 2017[8] showed comparable protective efficacy between mefloquine, atovaquone-proguanil and doxycycline. **Parasitaemia (*P. falciparum*):** Tickell-Painter *et al.,* 2017[8]: • Mefloquine vs placebo: 9.8% vs 60.2%; NNT 2, 95% CI 1.7 to 2.3; RR 0.18, 95% CI 0.06 to 0.55; 3 RCTs; n=414; I^2=80%), *low certainty evidence.* Soto et al., 2006 (n=144)[9]: • Atovaquone-proguanil vs placebo: atovaquone-proguanil was 100% effective in reducing parasitaemia; *low certainty evidence.* Weiss et al., 2011 (n=66)[11]: • Doxycycline vs placebo: 8/32 vs 34/34; NNT 4 (95% CI 3 to 10), *low certainty evidence* **Clinical cases of malaria (*P. falciparum*):** Tickell-Painter *et al.,* 2017[8]: • Mefloquine vs placebo: 1.4% vs 21.0%; NNT 6, 95% CI 5 to 7; RR 0.09, 95% CI 0.04 to 0.19; I^2=53%), *low certainty evidence.* • Mefloquine vs atovaquone-proguanil: no clinical cases of malaria with either agent in 2 RCTs, *low certainty evidence.* • Mefloquine vs doxycycline: 4/378 vs 3/366; RR 1.35, 95% CI 0.35 to 5.1; 4 RCTs; n=744; I2=3%, *low certainty evidence.* Weiss et al., 2011 (n=66)[11]: • Doxycycline vs placebo: 2/32 vs 20/30; NNT 16 (95% CI -47 to 7), *low certainty evidence*
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Uncertain ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	• Tickell-Painter *et al.,* 2017[8], reported that people were less likely to be non-adherent with atovaquone-proguanil compared to mefloquine due to adverse effects *(high-certainty evidence);* but equally as likely to be non-adherent as those taking doxycycline *(low-certainty evidence).* • Mefloquine users experienced more abnormal dreams, insomnia, anxiety and depressed mood compared to atovaquone-proguanil users *(moderate-certainty evidence)* or doxycyline *(very low-certainty evidence).* • Doxycycline users were more likely to have dyspepsia, photosensitivity, vomiting, and vaginal thrush *(very low-certainty evidence).*
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** • Mefloquine: Large ☐ Moderate ☒ Small ☐ None ☐ • Atovaquone-proguanil: Large ☐ Moderate ☐ Small ☒ None ☐ • Doxycyline: Large ☐ Moderate ☒ Small ☐ None ☐	Refer to the evidence tables and narrative, above.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐	The interventions are protective against malaria, but mefloquine, atovaquone-proguanil and doxycycline have adverse-effects – mefloquine (neurological adverse effects) and doxycycline (gastrointestinal adverse effects), more so than atovaquone-proguanil.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes: x* No: Uncertain: *Except mefloquine, as discontinued, from the South African market.	• Doxycycline: Currently listed on the national EML, and Appears as effective as the alternatives, without more adverse effects. Registered, readily available and inexpensive. • Atovaquone-proguanil: SAHPRA–registered, but not included on the national EML. Affordability may be an issue (see below). • Mefloquine: SAHPRA–registered, but recently withdrawn from the South African market.
RESOURCE USE	**How large are the resource requirements?** More intensive: x Less intensive: Uncertain:	**Price/treatment course for 1 week trip for adults (average weight 70kg adult):**

	Doxycycline	Atovaquone-proguanil
Dose	Initiate 2 days before travel & continue for 4 weeks after	Initiate 2 days before travel & continue for 7 days after
Dosing	Daily	Daily
Doses / trip	1 week trip: 37 3-week trip: 51	1 week trip: 16 3-week trip: 30
Dose	100mg caps/tabs	250mg/100mg caps/tabs
Unit price	R0.30*	R19.68**
Cost / trip	1 week trip: R11.10 3-week trip: R15.30	1 week trip: R314.88 3-week trip: R590.40

* Average weighted price for doxycycline 100mg = R0.30 (contract circular HP02-2019AI, accessed 18 May 2021)
** 60% of SEP - SEP database, 30 December 2020 – accessed 16 April 2021

Estimated budget impact:
Assumptions:
1. Migrant workers travel solely between work and home, and not with their families.
2. Data on annual case-load received from SAMEC was used to estimate the number of travelers who would require malaria chemoprophylaxis.

Limitations:
1. Data on number of cases reported shared by SAMEC has not been validated and there may be under-reporting of malaria cases (no other data available to estimate the number of travelers who would require malaria chemoprophylaxis – thus, a sensitivity analysis was done as shown below).
2. Model does not consider impact of other malaria preventative measures.
3. Model does not factor in pregnant women or children.

Based on the annual case load report for 2019/2020 from SAMEC***, the estimated budget impact (+/-20% upper and lower limits) is as follows:

Total cases reported	20 959	
Medicine	Doxycycline (1 week trip)	Atovaquone-proguanil
Estimated budget impact		
- 1 week trip	R 232 650 (R186K to R279K)	R 6 599 570 (R5.2 mil to R7.9 mil)
- 4-week trip	R 320 670 (R257K to R385K)	R 12 374 200 (R9.9 mil to R14.85 mil)

*** NDoH data on file (60% of total cases were imported cases)

International benchmarking:

Medicine	Doxycycline 100mg cap/tab	Atovaquone-proguanil cap/tab
MSH Price - Median Price[1]	US$ 0.0192 (Buyer price)	US$ 4.1648 (Supplier: Durbin (PLC) UK - EXW)
ZAR[2]	R 0.28	R 64.83

[1]International Medical Products Price Guide (2015) available at: https://www.msh.org/resources/international-medical-products-price-guide (accessed 18 May 2021)
[2] OANDA currency converter – average for Nov 2020 to May 2021: US$: ZAR = 14.826 - available at: https://www1.oanda.com/currency/converter/ (accessed 18 May 2021)

WHO EML listing (2021):
Only doxycycline 100 mg (solid dosage form) is listed for chemoprophylaxis of *Plasmodium falciparum.*
https://list.essentialmeds.org/

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [x] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	The chemo- prophylactic options that have been reviewed, are recommended in guidelines. Dosing convenience and side effects may impact how much people value the different options. Mefloquine has shown an advantage in terms of once weekly dosing. However, it is not available in South Africa and is associated with neurological adverse effects. Atovaquone-proguanil, dosed daily, needs to be continued for a week after returning from endemic area while daily dosed doxycycline must be continued for 4 weeks, which might affect patient adherence. Despite a lack of local survey data, the Committee was of the opinion that malaria chemoprophylaxis would be acceptable by both clinicians/healthcare workers and patients.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [x] Uncertain [ ]	Generally, equity would depend on access and capacity to deliver the intervention to public sector patients particularly migrant workers traveling to endemic areas, irrespective of South African resident status. Note that access to chemoprophylaxis for vulnerable populations (i.e., children and pregnant women) will be a challenge – doxycycline is contra-indicated in pregnant women and children<8 years of age[14] However, guidelines generally recommend that these vulnerable populations should avoid travelling to malaria-endemic areas.

Version	Date	Reviewer(s)	Recommendation and Rationale
First	14 June 2021	JN, PN, MR, TL	Doxycycline recommended for malaria chemoprophylaxis in children ≥ 8 years of age and in adults (excluding pregnancy), as available evidence shows that doxycycline reduces parasitemia and clinical malaria due to *P falciparum*. Mefloquine is currently unavailable in South Africa, and atovaquone-proguanil is currently unaffordable.

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[13] Nosten F, ter Kuile F, Maelankiri L, et al. Mefloquine prophylaxis prevents malaria during pregnancy: a double-blind, placebo-controlled study. J Infect Dis. 1994 Mar;169(3):595-603. https://pubmed.ncbi.nlm.nih.gov/8158032/
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South African National Essential Medicine List
Primary Health Care Medication Review Process
Rapid Review report
Component: Infections – malaria *(P. falciparum infection)*

TITLE: SINGLE, LOW-DOSE PRIMAQUINE WITH AN ARTEMISININ-BASED TREATMENT TO REDUCE *P. FALCIPARUM* MALARIA TRANSMISSION: EVIDENCE REVIEW OF CLINICAL BENEFITS AND HARMS

Date: 25 January 2021

Research question: Does the addition of single low-dose primaquine to artemisinin-based treatment for *P. falciparum* malaria reduce disease transmission?

Key findings

- We conducted a rapid review of available clinical evidence on the efficacy and safety of single low-dose primaquine (SLD PQ) with an artemisinin-combination treatment (ACT) to reduce *P.falciparum* malaria transmission.
- We found an Individual Participant Data (IPD) meta-analysis (n=2574 subjects; 14 RCTs up to and including 30 June 2018) that assessed the effect of SLD PQ + ACT on gametocyte carriage, and a Cochrane systematic review (24 RCTS and one quasi-RCT; up to 21 July 2017) that assessed the effect of SLD PQ + ACT on infectiousness and the risk of haemolysis. We also included an RCT published after the systematic reviews, that assessed the safety and tolerability of SLD PQ + ACT for *P. falciparum* in terms of the risk of haemolysis in patients with G6PD deficiency.
- IPD meta-analysis showed that SLD (0.25 mg/kg) PQ has the potential to block transmission in combination with ACT. The effectiveness of the combination on gametocyte persistence and infectivity is dependent on the type of ACT (artemether-lumefantrine produced better results compared to dihydroartemisinin-piperaquine).
    - SLD PQ reduced PCR-determined gametocyte carriage compared to those not treated with PQ on days 7 (23.4% (258/1101) vs 57.4% (316/551)) and 14 (11.4% (106/931) vs. 42.9% (202/471)) in patients presenting with gametocytemia on day 0.
- The Cochrane review showed that SLD PQ reduced infectiousness on day 3 or 4 from 14% to 2% and on day 8 from 4% to 1% when compared to no PQ in combination with ACT.
- The RCT reviewed showed that SLD PQ is well tolerated and appears safe in G6PD deficient (G6PDd) patients.
- The evidence suggests that SLD PQ safely reduces malaria transmission with no evidence of severe haemolysis, even in G6PDd patients.

PHC/ADULT HOSPITAL LEVEL ERC AND NEMLC RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: The PHC/Adult Hospital Level Committee recommends that single low-dose primaquine (0.25mg/kg), be added to artemisinin-based treatment for *P. falciparum* malaria, to reduce transmission. Pre-testing for G6PD deficiency is not required unless there is a clinical indication.
Rationale: Evidence of efficacy and safety for SLD primaquine for reducing gametocyte carriage.
Level of Evidence: II Moderate certainty evidence
Review indicator: Evidence of reduced community transmission

However, the NEMLC reviewed the evidence presented by the PHC/Adult Hospital Level Committee and recommended the following (see below):

NEMLC MEETING 25 FEBRUARY 2021:

NEMLC Recommendation: NEMLC acknowledges that there is reasonable evidence showing that primaquine, single dose (SLD), reduces gametocyte carriage. However, there is uncertainty regarding the actual effect on reduction of transmission and malaria eradication *(South African Malaria Elimination Committee was engaged, but no further evidence was forthcoming).* As SAHPRA registration of this product is currently underway, NEMLC recommends that including primaquine SLD on the national EML is premature for use from primary level of care. However, this will be revisited once the product is SAHPRA registered.

Rationale: Routine section 21 access at primary level of care, specifically by nurse prescribers, of an essential medicine is problematic in terms of continuous availability and consistency of price.

Review indicator: Availability of SAHPRA registered primaquine products.

BACKGROUND

Current World Health Organization (WHO) Malaria Treatment Guidelines recommend treatment of children and adults with uncomplicated *P. falciparum* malaria (excluding pregnant women in their first trimester) with an artemisinin-based combination therapy (ACT). In low transmission areas, as part of malaria elimination or pre-elimination strategies and to limit transmission, WHO advises the addition of a single dose of 0.25mg/kg primaquine, except in pregnant women, infants aged < 6 months and women breastfeeding infants aged < 6 months.[1]

However, primaquine is not currently registered in South Africa. Accessing primaquine for this indication therefore requires approval from the South African Health Products Regulatory Authority (SAPHRA) in terms of section 21 of the Medicines and Related Substances Act. The National Malaria Programme (NMP) currently holds section 21 approval for the use of single low-dose primaquine in low-transmission districts approaching malaria elimination.

The objective of the review is to review evidence for safety and efficacy of single low-dose primaquine when given with artemisinin-based combination therapy (ACT) in reducing the transmission of malaria. A particular safety concern is the risk of haemolysis in patients with glucose 6 phosphate dehydrogenase (G6PD) deficiency, when treated with single, low-dose primaquine.

Introduction

Malaria is caused by one of five species of *Plasmodium* parasites, transmitted by the bites of infected female *Anopheles* mosquitoes. *P. falciparum*, one of the plasmodium species, poses the greatest threat to humans. In 2018 the WHO reported that, *P. falciparum* accounted for 99.7% of estimated malaria cases in the WHO African Region.[2]

Gametocytes represent the sexual reproductive phase of the malaria parasite that facilitate the transmission of the parasite from humans to the *Anopheles* mosquito. ACT is efficacious at eliminating asexual parasites and early gametocytes but not very effective against mature stage *P. falciparum* gametocytes. Mature gametocytes can remain infectious for up to 2 weeks, supporting the transmission of malaria from humans to mosquitoes. By clearing the mature gametocytes, primaquine reduces the transmission of malaria.[3] (Figure 1)[4]

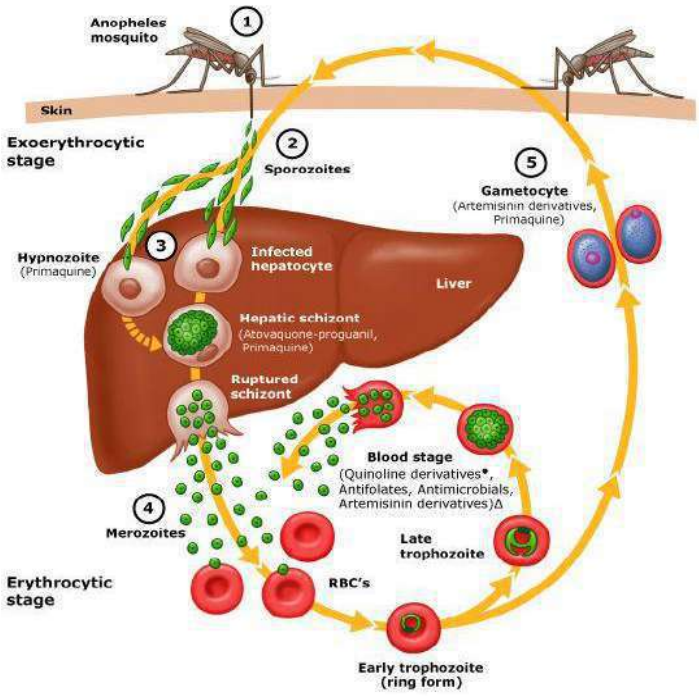

Figure 1: Lifecycle of the Malaria Paracyte Showing the Gametocyte Stage, the Point at Which Antimalarials (Artemisinin-Based Combination Therapy and Primaquine) Work

Sourced from: Hill AV. Vaccines against malaria. Philos Trans R Soc Lond B Biol Sci. 2011 Oct 12;366(1579):2806-14.[4]

WHO recommends single low-dose primaquine (SLD PQ) to reduce malaria transmission in low-transmission areas.[Error! Bookmark not defined.] The National Malaria Programme in South Africa is committed to eliminating malaria by 2023, as outlined in the Elimination Strategic Plan for South Africa 2019-2023.[5] Despite high coverage (>85%) of indoor residual spraying (IRS), additional efforts are needed to achieve malaria elimination in South Africa. One of those additional efforts is the provision of SLD PQ. To be practical, primaquine needs to be effective after a single dose administration, linked to ACT administration, and safe in all patients (including those with glucose 6 phosphate dehydrogenase (G6PD) deficiency). Based on available research evidence, the WHO currently recommends that G6PD testing is not required before administration of SLD PQ. [6, 7]

Preliminary results from a pilot study conducted in two malaria endemic provinces in South Africa showed promising results for the addition of SLD PQ. In the pilot study, 2783 patients were treated with SLD PQ (2097 in Nkomazi sub-district, Mpumalanga, & 686 in uMkhanyakude District, KwaZulu-Natal). In addition, 42 patients (9 in Bushbuckridge, Mpumalanga, and 33 in Greater Giyani, Limpopo) were treated with SLD PQ in the joint COVID-19-malaria screen, test and treat programmes between 20 April and 16 July 2020. A total of 1577 patients were traced for case investigation (1388 in Mpumalanga, 146 in KwaZulu-Natal and all 42 in the joint COVID-19 malaria screen, test and treat programme in Greater Giyani, Limpopo and Bushbuckridge, Mpumalanga). In Nkomazi, Mpumalanga, 17 (1.2%) of patients reported that they were "still ill", with a wide range of symptoms described, most of which could be malaria related. Symptoms reported were fever (n=2), body pain (6), sweating (1), shivering / "hot and cold" (4), "poor appearance" (1), loss of appetite (1), diarrhoea (1), and a nose bleed (1). Seven of these 17 patients were followed-up while they were still taking their 3-day artemether-lumefantrine treatment course. In uMkhanyakude, KwaZulu-Natal, 6 patients reported that they were "still ill"; 2 complained of "body pains", 1 complained of loss of appetite, 1 complained of fever and the remaining 2 patients did not specify their complaints. Five of these 6 patients were followed-up while they were still taking their 3-day artemether-lumefantrine treatment course. In the joint COVID-19-malaria campaign in Bushbuckridge, Mpumalanga and Greater Giyani, Limpopo, all 42 patients reported that they were fully recovered. The researchers report that although most adverse events were mild and considered malaria-related, the gastrointestinal adverse effects were considered possibly related to primaquine.[8]

Raman *et al*. (2019) studied the addition of SLD PQ on day 3 to standard AL treatment for uncomplicated *P. falciparum* malaria in South Africa. Efficacy, safety, and tolerability were assessed on days 3, 7, 14, 28 and 42. The study results showed that no gametocytes were detected by either microscopy or PCR in any of the follow-up samples collected after randomization on day 3, preventing assessment of primaquine efficacy. In terms of safety, one third of the sample had a haemoglobin drop > 2 g/dL but this drop was not associated with PQ treatment. The drop was associated with G6PD genotype (52.9% (9/17)) with A− genotype vs. other genotypes (31% (36/116); p = 0.075). This study included a

small sample and study population, which might have been skewed toward nourished individuals who sought care by day 3. However, the RCT showed that from a safety perceptive SLD PQ can be implemented without G6PD testing to advance malaria elimination in South Africa.[9]

The following review summarises the evidence for the use and effect on outcomes of interest of SLD PQ in combination with ACT compared to malaria treatment with an ACT alone in adults and children with uncomplicated *P. falciparum* malaria.

Eligibility criteria for review

Population: Adults or children with uncomplicated *P. falciparum* malaria, diagnosed by either microscopy or rapid diagnostic tests (except pregnant women, infants aged <6 months and women breastfeeding infants aged <6 months)

Intervention: Single low dose primaquine (0.75mg/kg or less) in combination with artemisinin-based regimens

Comparators: Treatment with an artemisinin-based regimen alone

Outcomes:
Efficacy: Transmission potential, assessed by weekly gametocyte carriage using molecular methods and/or by membrane feeding assay conducted on day 0 and any day post treatment (measures of community transmission - mosquito infectivity); incidence of *P. falciparum malaria* at community level
Safety: serious adverse events, particularly incidence of severe haemolysis in treated patients

Study designs: Systematic reviews of randomised controlled trials (RCTS) and individual RCTs

METHODS

We conducted a rapid review of the evidence by systematically searching three electronic databases (Cochrane library, PubMed and Epistemonikos) on 8 December 2020. We included systematic reviews, where possible with meta-analyses of randomised controlled trials (RCTs), and individual RCTs (for studies not included in the relevant systematic reviews). We excluded observational studies, case reports, case series and narrative reviews. Publications were restricted to those published in English. The search strategy is shown in Appendix 1. Two reviewers screened records and extracted data (TL & MR). Screening of records was done independently and in duplicate (TL, MR), with disagreement resolved through discussion. Excluded studies with the rationale for exclusion are summarised in Table 1; whilst relevant study data were extracted in a narrative table of results (TL, MR), with results reviewed and checked by the third reviewer (AG). AG reviewed the overall report.

The quality of evidence was assessed independently using the AMSTAR 2 tool[10] for systematic reviews (MR, TL) and GRADE assessment[11] for RCTs (MR, TL), as required.

RESULTS

Results of search
After the removal of 3 duplicates, two reviewers (TL, MR) screened 21 records and identified a Cochrane review (Graves et al, 2018[12]), an individual participant data (IPD) meta-analysis (Stepniewska *et al*, 2020[13]) and an RCT (Dysoley *et al*, 2019[14]). The RCT was published after the date of the last search performed for the systematic review by Stepniewska *et al.* (30 June 2018). Some of the RCTs included in the Cochrane review were also included in the IPD meta-analysis.

Description of the studies

Individual participant analysis:[13]
Stepniewska et al., 2020 conducted an individual patient meta-analysis (n=2574; 14 studies) to evaluate the gametocytocidal and transmission-blocking efficacy of PQ in combination with different ACTs. i.e., to quantify PQ effect on (1) gametocyte carriage in the first 2 weeks post treatment; and (2) the probability of infecting at least 1 mosquito or of a mosquito becoming infected.

- *Study Results*:
  - **Gametocyte carriage**: PQ treatment reduced PCR-determined gametocyte carriage compared to those not treated with PQ on days 7 (23.4% (258/1101) vs 57.4% (316/551)) and 14 (11.4% (106/931) vs. 42.9% (202/471)) in patients presenting with gametocytemia on day 0 (odds ratio [OR], 0.22; 95% confidence interval [CI]: 0 .17 to 0.28 & OR 0.12; 95% CI: 0.08 to 0.16, respectively). The rate of decrease of gametocyte carriage was faster when PQ was combined with artemether lumefantrine (AL) compared to dihydroartemisinin-piperaquine (DP) (P = .010 at day 7).
  - **Transmission to mosquitoes:** in 3 of 14 studies mosquito infections were rarely observed 1 week after administration of 0.25 mg/kg PQ (irrespective of other drugs) – as a surrogate marker for community transmission.

- *Quality of evidence:*
  - Risk of observer bias was low because laboratory personnel performing molecular assays for dissecting mosquitoes were blinded in all studies related to gametocyte carriage, only one of the 14 studies was sequential in design, and for all but one study the randomization method was computer generated or envelope drawn.
  - Only 3 studies of 14 reviewed transmission to mosquitoes, limiting the conclusion that mosquito infections were rarely observed 1 week after administration of 0.25 mg/kg PQ.

The IPD showed that 0.25 mg/kg PQ has the potential to block transmission in combination with ACT. The effectiveness of the combination on gametocyte persistence and infectivity is dependent on the type of ACT (AL producing better results compared to DP) used in combination with PQ.

Cochrane review[12]:

This systematic review of 24 RCTS and one quasi-RCT (up to 21 July 2017) assessed whether single dose PQ added to artemisinin-based combination treatment (ACT) for falciparum malaria reduced disease transmission. The investigators found no cluster-randomised studies measuring malaria transmission intensity (prevalence or incidence of malaria infection; or entomological inoculation rate), which would give direct evidence for malaria transmission. Therefore, indirect evidence from feeding studies or measurement of reduced *P. falciparum* gametocytaemia was considered to determine infectiousness (people infectious and mosquitoes infected) amongst those assigned to PQ compared with those who were not. Trials were stratified according to PQ dose (low, 0.2 to 0.25 mg/kg; moderate, 0.4 to 0.5 mg/kg; and high dose, 0.75 mg/kg).

- *Study results:*
  - **Infectiousness,** with low dose PQ was reduced on day 3 or 4 from 14% to 2% and on day 8 from 4% to 1% when compared to no PQ, in combination with ACT (low certainty evidence) – with waning infectiousness in the control group by day 8. Infectiousness was similarly reduced with moderate dose PQ on day 3 or 4 from 14% to 2% and on day 8 from 4% to 1% when compared to no PQ, in combination with ACT (low certainty evidence). Infectiousness was reduced with high-dose PQ on day 3 and 4 from 10% to 2% and on day 8 from 5% to 1% (low certainty evidence). Low dose (SLD) PQ appeared to be as effective as higher doses (moderate and high dose PQ).– see Table 1.
  - **Gametocytes detected by PCR**, low dose PQ had little or no effect at day 3 or 4 (moderate certainty evidence); with a reduction at day 8 (RR 0.52, 95% CI: 0.41 to 0.65; high certainty evidence). Moderate- and high-dose PQ had a similar effect to low-dose PQ on gametocyte prevalence – see Table 1.
  - **Severe haemolysis** associated with low-dose PQ was infrequent (12.3% vs 13.2% in the control group; RR 0.98, 95% CI: 0.69 to 1.39; moderate certainty evidence), although small numbers of patients with G6PD deficiency were included. Moderate dose PQ was probably associated with severe haemolysis (2% in no PQ vs 4% with moderate dose PQ); whilst there were no reports for severe haemolysis in the high-dose PQ studies reviewed.

- *Quality of evidence:*
  - An AMSTAR 2 review of the Cochrane Review confirmed that the methodological quality of the review was of high quality.
  - For the meta-analyses, where there was heterogeneity between trials, so the random-effect model (rather than the fixed-effects model) was used to estimate the risk ratios.

- Evidence was graded as low certainty for comparisons on infectiousness mostly due to imprecision and small sample sizes.
- Risk of bias for individual RCTs was assessed as low to moderate, with more than half of the RCTs assessed as low risk, and 20% assessed as high risk; whilst the remainder of the RCTs (mostly older RCTs) did not report sufficient information for assessment. The highest risk of bias was inadequate blinding of study participants and personnel. There were also insufficient trials to conduct a sensitivity analysis of the quality of the RCTs.
- Publication bias was not assessed due to insufficient trials within each comparison.

The Cochrane review concluded that low-dose PQ reduced infectiousness with no evidence of harm, but whether this reduction translates to reduced malaria transmission needs to be verified in community-level studies.

Randomised controlled study:

One RCT was reviewed, that studied low-dose PQ in combination with ACT vs no addition of PQ. Dysoley et al., 2019[14] evaluated the tolerability of single low dose PQ in Cambodia (n=109). The primary outcome of interest was day 7 hemoglobin (Hb) concentration. Secondary outcomes of interest included D7-D0 absolute and fractional falls in Hb, modelled Hb changes over time, total malaria attributable fall (MAFt), D28Hb-nadir Hb, Hb recovery (D28 Hb > D0 Hb concentration), G6PD geno- and phenotype, thalassemia type, D28 cure rate, gametocyte carriage, and PQ, carboxy PQ, and PP concentrations.

- *Study results:*
  - **Severe haemolysis - Day 7 Hb concentration:** Mean nadir Hb occurred on D7 [11.6 (range 6.4 to 15.6) g/dL] and was significantly lower (p = 0.040) but not clinically significant in terms of acute haemolytic anaemia in glucose-6-phosphate dehydrogenase deficiency (G6PDd) (n = 9) vs. G6PDn (normal G6PD) (n = 46) DHAPP+SLDPQ recipients: 10.9 vs. 12.05 g/dL, Δ = -1.15 (95% CI: -2.24 to -0.05) g/dL.
- *Quality of evidence:*
  - The main study limitation was the very small number of G6PDd patients.

Single dose PQ is tolerated and may be safe in G6PDd patients.

CONCLUSION

The Cochrane review showed that SLD PQ may reduce infectiousness and is safe with no evidence of severe haemolysis. The subsequent IPD meta-analysis quantified the ability of SLD PQ, given in combination with ACT, to clear gametocytes and to potentially reduce malaria transmission. Studies measuring malaria transmission intensity (prevalence or incidence of malaria infection; or entomological inoculation rate) would further verify SLD PQ's effectiveness in reducing malaria transmission.

Reviewer(s): Dr M Reddy, Ms TD Leong, Mr A Gray, Dr T Kredo

Declaration of interests: MR (Better Health Programme, South Africa), TDL (National Department of Health, Affordable Medicines Directorate, Essential Drugs Programme) and TK (Cochrane South Africa, South African Medical Research Council) have no interests to declare in respect of primaquine for malaria. AG (Division of Pharmacology, University of KwaZulu-Natal) is a member of the South African Malaria Elimination Committee.

Acknowledgement: Prof Karen Barnes (South African Malaria Elimination Committee) for providing the preliminary data from pilot study conducted in two malaria endemic provinces in South Africa[8].

Table 1: Excluded studies

Citation	Type of Record	Reason for Exclusion
Abba K et al. Rapid diagnostic tests for diagnosing uncomplicated non-falciparum or Plasmodium vivax malaria in endemic countries. Cochrane Database of Systematic Reviews. 2014	Cochrane review	Review on diagnostic tests
Sinclair D et al. Artemisinin-based combination therapy for treating uncomplicated malaria. Cochrane Database of Systematic Reviews. 2009	Cochrane review	Did not meet PICO criteria. Only 1 RCT reviewed Primaquine
Gogtay N et al. Artemisinin-based combination therapy for treating uncomplicated Plasmodium vivax malaria. Cochrane Database of Systematic Reviews. 2013	Cochrane review	Did not meet PICO criteria
Osei-Akoto A. Atovaquone-proguanil for treating uncomplicated malaria. Cochrane Database of Systematic Reviews. 2005	Cochrane review	Did not meet PICO criteria
Poirot E et al. Mass drug administration for malaria. Cochrane Database of Systematic Reviews. 2013	Cochrane review	Did not meet PICO criteria
Bradley et al. Clin Infect Dis. 2019 Sep 27;69(8):1436-1439. doi: 10.1093/cid/ciz134. Transmission-blocking Effects of Primaquine and Methylene Blue Suggest Plasmodium falciparum Gametocyte Sterilization Rather Than Effects on Sex Ratio.	RCT (Pubmed)	Report
Mendes Jorge M et al. PLoS One. 2019 Oct 10;14(10):e0222993. doi: 10.1371/journal.pone.0222993. eCollection 2019. Safety and efficacy of artesunate-amodiaquine combined with either methylene blue or primaquine in children with falciparum malaria in Burkina Faso: A randomized controlled trial.	RCT (Pubmed)	Did not meet PICO criteria
Raman J, et al. Safety and tolerability of single low-dose primaquine in a low-intensity transmission area in South Africa: an open-label, randomized controlled trial. Malar J. 2019 Jun 24;18(1):209. doi: 10.1186/s12936-019-2841-8.	RCT (Pubmed)	RCT data pooled in the IPD by Stepniewska *et al* (2020).
Phommasone K et al. PLoS One. 2020 Feb 5;15(2):e0228190. doi: 10.1371/journal.pone.0228190. eCollection 2020. Mass drug administrations with dihydroartemisinin-piperaquine and single low dose primaquine to eliminate Plasmodium falciparum have only a transient impact on Plasmodium vivax: Findings from randomised controlled trials.	RCT (Pubmed)	Did not meet PICO criteria
Sutanto I et al. Clin Infect Dis. 2018 Oct 15;67(9):1364-1372. doi: 10.1093/cid/ciy231. Negligible Impact of Mass Screening and Treatment on Mesoendemic Malaria Transmission at West Timor in Eastern Indonesia: A Cluster-Randomized Trial.	RCT (Pubmed)	Did not meet PICO criteria
von Seidlein L. PLoS Med. 2019 Feb 15;16(2):e1002745. doi: 10.1371/journal.pmed.1002745. eCollection 2019 Feb. The impact of targeted malaria elimination with mass drug administrations on falciparum malaria in Southeast Asia: A cluster randomised trial.	RCT (Pubmed)	Did not meet PICO criteria
Phommasone K et al. Malar J. 2020 Jan 3;19(1):4. doi: 10.1186/s12936-019-3091-5. The use of ultrasensitive quantitative-PCR to assess the impact of primaquine on asymptomatic relapse of Plasmodium vivax infections: a randomized, controlled trial in Lao PDR.	RCT (Pubmed)	Did not meet PICO criteria
Hsiang MS. Lancet. 2020 Apr 25;395(10233):1361-1373. doi: 10.1016/S0140-6736(20)30470-0. Effectiveness of reactive focal mass drug administration and reactive focal vector control to reduce malaria transmission in the low malaria-endemic setting of Namibia: a cluster-randomised controlled, open-label, two-by-two factorial design trial.	RCT (Pubmed)	Did not meet PICO criteria
Pongvongsa T, et al. The dynamic of asymptomatic Plasmodium falciparum infections following mass drug administrations with dihydroarteminisin-piperaquine plus a single low dose of primaquine in Savannakhet Province, Laos. Malar J. 2018 Nov 3;17(1):405.	RCT (Pubmed)	Did not meet PICO criteria
Shekalaghe S et al. Optimal timing of primaquine to reduce Plasmodium falciparum gametocyte carriage when co-administered with artemether-lumefantrine. Malar J. 2020 Jan 21;19(1):34. doi: 10.1186/s12936-020-3121-3.	RCT (Pubmed)	RCT data pooled in the IPD by Stepniewska *et al.* (2020).
Commons RJ et al. Risk of Plasmodium vivax parasitaemia after Plasmodium falciparum infection: a systematic review and meta-analysis. Lancet Infect Dis. 2019 Jan;19(1):91-101.	Systematic review (Epistemonikos)	Risk of Plasmodium vivax parasitaemia
Graves PM, et al. Primaquine or other 8-aminoquinolines for reducing Plasmodium falciparum transmission. Cochrane Database Syst Rev. 2018 Feb 2;2(2):CD008152.	Systematic review (Epistemonikos)	Duplicate, record also retrieved in Cochrane database search
Haeusler IL, et al. The arrhythmogenic cardiotoxicity of the quinoline and structurally related antimalarial drugs: a systematic review. BMC Med. 2018 Nov 7;16(1):200.	Systematic review (Epistemonikos)	Did not meet PICO criteria

RCT = Randomized Control Trial

Table 2: Characteristics of reviewed studies

i) Individual participant data (IPD) analysis

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments

Stepniewska et al., 2020	Systematic Review and IPD	n=2574
		
		14 studies
		
		Studies mainly from Africa
			Single dose primaquine (PQ) + Artemether-lumefantrine (AL) **or** dihydroartemisinin-piperaquine (DP), artesunate-sulfadoxine-pyrimethamine (ASSP) and (sulfadoxine-pyrimethamine-amodiaquine	Gaemtocytemia	***PQ vs no PQ***
					<u>Gametocytaemia in non-detectable gametocytes at baseline:</u>
					• 12.9% (39/302) vs 19.6% (35/179) (OR 0.55; 95% CI, 0.32 to 0.96; P = 0.035)
					• Similar effect of PQ on gametocyte appearance (P = 0.308) between day 7 (D7) (OR, 0.58; 95% CI, .33 to 1.01; P = .053) & D14 (OR, 0.30; 95% CI,0 .14 to 0.63; P = .002).
					<u>Gametocytaemia in detectable gametocytes at baseline:</u>
					• 23.4% (258/1101) on D7 vs 57.4% (316/551) (OR, 0.22; 95% CI, .17–.28; P < .001).
					• Higher dose of PQ was associated with lower prevalence of gametocyte positivity on D7 & D14 (AOR, 0.69; 95% CI, .65–.74 and AOR, 0.58; 95% CI, .53–.64 for each 0.1-mg/kg increase in dose, respectively; both P < .001). AOR of 0.40 (95% CI, .34–.46) for D7 gametocyte carriage vs AOR 0.26 (95% CI, .20–.33) for D14 gametocyte carriage
					• Addition of PQ reduced gametocyte carriage for both ACTs, differed between AL and DP (test for interaction, P = .010 for D7 & P < .001 for D14).
					  ○ AL -reduction in gametocyte carriage probability achieved with 0.25-mg/kg PQ dose,
					  ○ DP - higher doses of PQ were associated with additional substantial reductions in gametocyte carriage.
					• 0.25 mg/kg PQ + AL reduced risk of gametocytemia on D7 to 26.0% (95% CI, 18.7%–34.9%) and D14 to 7.6% (95% CI, 4.3%–13.2%) vs 37.1% (95% CI, 27.6%–47.8%) & 18.2% (95% CI, 11.4%–27.9%) with DP. Gametocyte carriage risk significantly higher on D7 in patients treated with PQ on D2 or 3 vs patients treated with PQ on day 0 (AOR, 2.28; 95% CI, 1.66–3.69; P < .001). Not statistically significant by D14 (AOR, 1.74; 95% CI, .80–3.81; P = .164)
					<u>Gametocyte density</u>
					• Median values of 2.0% (interquartile range [IQR], 0.3%–10.2%) vs baseline by D7 vs 29.8% (IQR, 8.1%–77.4%) (P < .001). Values on D14 were 0.5% (IQR, 0.1%–5.6%) vs 9.6% (IQR, 1.5%–36.0%) (P < .001)
						• Risk of bias is low - blinding on all measurements of gametocyte carriage.
						
						AMSTAR assessment of the systematic review:
						Moderate quality.
						• Research questions and inclusion criteria for the review included the components of PICO? Yes
						• Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? Yes
						• Review authors explained selection of the study designs for inclusion in the review? Yes
						• Review authors used a comprehensive literature search strategy? Partial yes
						• Review authors perform study selection and data extraction in duplicate? Yes
						• Review authors provided a list of excluded studies and justify the exclusions? No
						• Review authors described the included studies in adequate detail? Yes
						• Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? Yes
						• Review authors reported on the sources of funding for the studies included in the review? No
						• For meta-analyses, review authors used appropriate methods for statistical combination of results? Yes
						• For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis? Yes

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
						• Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review? Yes • Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? No • For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review? No • Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review? Yes • Reviewed effect of PQ single dose (0.0625 to 0.75 mg/kg) on transmission potential of *falciparum malaria* infections, when coadministered with schizonticidal drugs. • Single dose PQ has gametocyte clearing and sterilizing effects. • Mosquito infections were rarely observed 1 week after administration of PQ (irrespective of other drugs) - caution - only in 3/14 studies

ACT= artemisinin-based containing therapy; Day=D; PQ = primaquine; RCT=randomised controlled trial; RR=risk ratio

ii) Systematic review:

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
Graves et al, 2018	Systematic review of 24 RCTs and 1 quasi-RCT 14 RCTs evaluated ACT; 9 RCTs evaluated	*Study participants:* Adults or children with *P. falciparum* infection or a mixed infection of *P. falciparum* and other *Plasmodium* species treated with ACT	PQ with ACT ***vs*** no PQ *PQ doses varied:* • low: 0.2 to 0.25 mg/kg • moderate: 0.4 to 0.5 mg/kg	• Infectiousness (people infectious and mosquitoes infected) • Potential infectiousness (gametocyte measures assessed by microscopy or PCR) • Severe haemolysis	***PQ (+ACT) vs no PQ*** <u>Infectiousness, day 3 or 4:</u> *Low dose:* RR 0.12, 95%CI 0.02 to 0.88, 3 RCTs; n=105; 2% vs 14% (*low certainty evidence*) *Moderate dose:* RR 0.13, 95% CI 0.02 to 0.94; 3 RCTs, n=109 (low *certainty evidence*)	There was a paucity of direct evidence for malaria transmission, as no community cluster-RCTs measuring malaria transmission intensity (prevalence or incidence of malaria infection; or entomological inoculation rate) could be sourced. Thus, indirect evidence from feeding studies or measurement of reduced *P. falciparum* gametocytaemia was considered reasonable to determine potential reduced infections acquired by

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
	non-ACT; 2 RCTs included both ACT and non-ACT arms 2 trial arms used bulaquine; 7 PQ arms used low dose of 0.2 to 0.25 mg/kg (6 with ACT); 11 PQ arms used moderate dose of 0.4 to 0.5 mg/kg (7 with ACT); remaining arms used high dose of 0.75 mg/kg	*Settings:* Mali, Burkina Faso, The Gambia, Tanzania, Senegal *G6PD status:* 11 RCTs excluded participants with G6PD deficiency; 1 RCT included only those with G6PD deficiency; and 3 RCTs included all, irrespective of status. 10 RCTs did not report on testing. *Time of follow-up* was restricted to eight days after treatment to enable maximum comparison between trials.	• high: 0.75 mg/kg		*High dose:* RR 0.2, 95% CI 0.02 to 1.68, 1 RCT, n=101 (*low certainty evidence*) <u>Infectiousness, day 8:</u> *Low dose:* RR 0.34, 95% CI 0.07 to 1.58, 4 RCTs, n= 243 participants; 1% vs 4% (*low certainty evidence*) *Moderate dose:* RR 0.33, 95% CI 0.07 to 1.57; 4 RCTs, n=246 (low *certainty evidence*) *High dose:* RR 0.18, 95% CI 0.02 to 1.41, 2 RCTs, n=181 (*low certainty evidence*) <u>Gametocytes detected by PCR, at day 3 or 4:</u> *Low dose:* RR 1.02, 95% CI 0.87 to 1.21; 3 RCTs; n=414 (*moderate certainty evidence*) *Moderate dose:* RR 1.09, 95% CI 0.93 to 1.28; 3 RCTS; n=418 (*moderate certainty evidence*) *High dose:* RR 0.92, 95% CI 0.75 to 1.13; 2 RCTS; n=394 (*low certainty evidence*) <u>Gametocytes detected by PCR at day 8</u>: *Low dose:* RR 0.52, 95% CI 0.41 to 0.65; 4 RCTs, n=532 (*high certainty evidence)* *Moderate dose:* RR 0.37, 95% CI 0.29 to 0.48; 5 RCTs; n=758 (*high certainty evidence)* *High dose:* RR 0.31, 95% CI 0.23 to 0.43; 5 RCTs; n=793 (*high certainty evidence)* <u>Severe haemolysis:</u>	mosquitoes from malaria-infected persons (infectiousness). AMSTAR assessment of the systematic review: **High quality.** • Research questions and inclusion criteria for the review included the components of PICO? Yes • Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? Yes • Review authors explained selection of the study designs for inclusion in the review? Yes • Review authors used a comprehensive literature search strategy? Yes • Review authors perform study selection and data extraction in duplicate? Yes • Review authors provided a list of excluded studies and justify the exclusions? Yes • Review authors described the included studies in adequate detail? Yes • Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? Yes • Review authors reported on the sources of funding for the studies included in the review? Yes • For meta-analyses, review authors used appropriate methods for statistical combination of results? Yes (Random- vs fixed-effects) • For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis? Yes • Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review? Yes • Review authors provided a satisfactory explanation for, and discussion of, any

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
					Low dose: RR 0.98, 95% CI 0.69 to 1.39; 4 RCTs, n=752 (*moderate certainty evidence)* *Moderate dose:* RR 1.54, 95% CI 0.38 to 6.30; 2 RCTs; n=260 (*low certainty evidence*) *High dose:* Trials did not systematically report evidence of haemolysis	heterogeneity observed in the results of the review? Yes • For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review? No • Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review? Yes Where heterogeneity between trials was observed, a randoms effect RR (rather than fixed RR) was estimated. Where evidence was graded as low certainty, this was mostly due to imprecision. Risk of bias was assessed as low to moderate, with >50% RCTs assessed as low risk, and 20% assessed as high risk; whilst the remainder of the RCTs (mostly older RCTs) did not report sufficient information for assessment. The highest risk of bias was inadequate blinding of study participants and personnel. There were also insufficient trials to conduct a sensitivity analysis of the quality of the RCTs. Publication bias was not assessed due to insufficient trials within each comparison.

RCT=randomised controlled trial; ACT= artemisinin-based containing therapy; PCR= polymerase chain reaction; PQ = primaquine; RR=risk ratio

iii) Randomised controlled study:

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
Dysoley et al., 2019	Open-label RCT	n= 109 ≥1 year, ≥7 kg with acute (≤ 48 h), symptomatic (≥ 38 °C axilla/≥ 37.5°C aural/history of fever), uncomplicated	Dihydroartemisinin-piperaquine (DHAPP) + single low-dose PQ (SLDPQ, 0.25 mg/kg) vs. DHAPP alone	Primary • D7 Hbconcentration	**G6PD deficiency (G6PDd) (n = 9)** **vs.** **G6PDn normal G6PD) (n = 46)** Hb Concentration: Mean nadir Hb occurred on D7 (11.6, 95% CI6.4 to 15.6 g/dL) & was significantly lower (p = 0.040) in G6PD deficiency (G6PDd) (n = 9) vs. G6PDn (normal G6PD) (n = 46)	• The main study limitation was the very small number of G6PDd patients • DHAPP+SLDPQ was associated with modest Hb declines in G6PD Viangchan, a moderately severe variant i.e. did not result in clinical significant haemolysis

		falciparum malaria (≥ 1 asexual form/500 WBCs) Cambodia			• DHAPP+SLDPQ recipients: 10.9 vs. 12.05 g/dL, Δ = -1.15 (95% CI: -2.24 to -0.05) g/dL. • 3 G6PDn patients had D7 Hb concentrations < 8 g/ dL; D7-D0 Hbs were 6.4to 6.9, 7.4 to 7.4, & 7.5 to 8.2 g/dl • All patients - mean HemoCue measured nadir Hb was 12.4 g/dL (D7) increasing to 13.1 g/dL by D28.	• Mean nadir Hb occurred on D7 & was significantly lower G6PDd vs. G6PDn but was not clinically significant in terms of acute haemolytic anemia • Evidence that SLDPQ is tolerated and appears safe in G6PDd patients

AS=Artesunate; AL=*Artemether & Lumefantrine; DP=Dihydroartemisinin-piperaquine; Hb=Haeomoglobin; PQ=Primaquine; SP=*Sulphadoxine*/pyrimethamine; WBCs=white blood cells*

Table 3: GRADE evidence profile

Question: Primaquine compared to no primaquine for reducing community transmission of malaria
Patient or population: reducing community transmission of malaria
Setting: Burkina Faso, Colombia, Kenya, Mali, South Africa, Sudan, Tanzania, The Gambia, Uganda
Intervention: primaquine
Comparison: no primaquine

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Primaquine	no primaquine	Relative (95% CI)	Absolute (95% CI)	
Community transmission (follow up: 7 days; assessed with: gametocyte carriage)											
14	randomised trials	not serious	not serious	not serious [a]	not serious	publication bias strongly suspected [b]	258/1101 (23.4%)	316/551 (57.4%)	**OR 0.22** (0.17 to 0.28)	**345 fewer per 1,000** (from 387 fewer to 300 fewer)	⊕⊕⊕◯ MODERATE
Community transmission (follow up: 14 days; assessed with: gametocyte carriage)											
11	randomised trials	not serious	not serious	not serious [a]	not serious	publication bias strongly suspected [b]	106/931 (11.4%)	202/471 (42.9%)	**OR 0.12** (0.08 to 0.16)	**346 fewer per 1,000** (from 372 fewer to 322 fewer)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; OR: Odds ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Studies conducted in higher transmission areas however the studies were sufficiently representative of the South African setting and we did not downgrade for indirectness
b. The IPD analysis could only include the available evidence from those willing or able to share study data.

Appendix 1: Search strategy

Cochrane library *Search:* "P. falciparum:ti,ab,kw AND primaquine:ti,ab,kw in Cochrane Reviews (Word variations have been searched)" **Records retrieved: 6 (5 was not related to the PICO and 1 SR included in the review)**
EPISTEMONIKOS **Search:** (title:((title:(p. falciparum) OR abstract:(p. falciparum))) OR abstract:((title:(p. falciparum) OR abstract:(p. falciparum)))) AND (title:(primaquine) OR abstract:(primaquine)) – from 2018 to 2020 **Records retrieved: 4 (1 was a duplicate, 2 were not related to the PICO and 1 IPD analysis included for review)**
PUBMED *Search:* ("plasmodium falciparum"[All Fields]) AND ("primaquine"[All Fields]) **Filters:** Randomized Controlled Trial, Humans, from 2018/07/01 - 2020/12/7 **Records retrieved: 11 (2 were duplicates, 8 were not related to the PICO and 1 RCT included in the review)**

Appendix 2: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ Low ☐ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	SLD PQ added to ACT for falciparum malaria to reduce infectiousness, gametocyte carriage, gametocyte PCR and disease transmission – reviewed evidence assessed overall as moderate (see table 1 for details): ***Stepniewska et al, 2020:*** • *Individual patient meta-analysis* of moderate to high quality. ***Grave et al, 2018:*** • *Participants' infectiousness at day 8 – PQ vs no PQ* – low quality evidence • *Participants with gametocytes at day 8 by PCR – PQ vs no PQ*: high quality evidence.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☒ Small ☐ None ☐	***Stepniewska et al, 2020:*** • *Gametocyte carriage by D7*: 0.25 mg/kg PQ combined with AL reduced risk of gametocytemia to 26.0% (95% CI, 18.7% to 34.9%) *vs* 37.1% (95% CI, 27.6% to 47.8%) with DP alone. • *Gametocyte carriage by D14*: 0.25 mg/kg PQ combined with AL reduced risk of gametocytemia to 7.6% *vs* 18.2% (95% CI, 11.4% to 27.9%) with DP alone. • Gametocyte carriage risk reduction is influenced more positively on D7 if PQ is given on D0 vs D2 or D3: AOR, 2.28; 95% CI, 1.66 to 3.69; P < 0.001; though not statistically significant by D14. ***Grave et al, 2018:*** • *Participants' infectiousness at day 8 – PQ vs no PQ*: (4 RCTs, n=243) RR 0.34 (0.07 to 1.58); ARR 3% (95% CI -1.31% to 7.31%) • *Participants with gametocytes at day 8 by PCR – PQ vs no PQ*: (4 RCTs, n=532) RR 0.52 (0.41 to 0.65); ARR 22% (95% CI 9.05% to 34.95%) Paucity of RCTs measuring malaria transmission intensity (prevalence or incidence of malaria infection; or entomological inoculation rate) in endemic communities; and therefore RCTS showing a reduction of gametocytaenia with PQ combined with ACT vs ACT alone has been considered.

<table>
<tr><th></th><th>JUDGEMENT</th><th>EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE OF HARM</td><td>What is the certainty/quality of evidence?
High [ ] Moderate [X] Low [ ] Very low [ ]
High quality: confident in the evidence
Moderate quality: mostly confident, but further research may change the effect
Low quality: some confidence, further research likely to change the effect
Very low quality: findings indicate uncertain effect</td><td>See description of the quality of IPD analysis (Stepniewska et al, 2020), above.

The evidence in the Cochrane review (Grave et al, 2018) was downgraded from high to moderate certainty due to imprecision.</td></tr>
<tr><td>EVIDENCE OF HARMS</td><td>What is the size of the effect for harmful outcomes?
Large [ ] Moderate [ ] Small [X] None [ ]</td><td>Results from an IPD analysis, Cochrane systematic review show that SLD PQ is well tolerated and appears safe in both normal G6PD and G6PD-deficient patients.

See text above for details of the low risk of severe haemolysis/acute haemolytic anaemia with SLD PQ.</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable harms?
Favours intervention [X] Favours control [ ] Intervention = Control or Uncertain [ ]</td><td></td></tr>
<tr><td>FEASABILITY</td><td>Is implementation of this recommendation feasible?
Yes [ ] No [ ] Uncertain [X]</td><td>Primaquine is currently not registered with SAHPRA and is accessed via S21 application.</td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [X] Less intensive [ ] Uncertain [ ]</td><td>Direct medicine price/ treatment dose/ adult:
<table>
<tr><th>Medicine</th><th>Dose</th><th>Acquisition price (ZAR)*</th></tr>
<tr><td>Primaquine 15mg, tablet</td><td>15mg</td><td>15.15</td></tr>
</table>
* S21 price accessed by UCT from Equity pharmaceuticals - Email communication on file.
Estimated budget impact:
S21 application (2021) = 11000**
Estimated incremental budget expenditure for SLD PQ = estimated R166650.00
** Shared by SAMEC (Jan2021 – Dec2021) – communication on file</td></tr>
<tr><td>VALUES, PREFERENCES, ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [ ] Major [ ] Uncertain [X]

Is the option acceptable to key stakeholders?
Yes [ ] No [ ] Uncertain [X]</td><td>No local survey data could be sourced to determine acceptability of technology by respective stakeholders.</td></tr>
<tr><td>EQUITY</td><td>Would there be an impact on health inequity?
Yes [ ] No [X] Uncertain [ ]</td><td>Primaquine access for reducing malaria transmission is only required in malaria endemic areas (i.e. lower socio-economic areas).</td></tr>
</table>

Version	Date	Reviewer(s)	Recommendation and Rationale
First	25 January 2021	MR, TL, AG	SLD primaquine (0.25mg/kg), not be recommended for addition to the national EML. for elimination of *P. falciparum* malaria. There is uncertainty regarding the actual effect on reduction of transmission and malaria eradication. Furthermore, primaquine is not currently SAHPRA-registered.

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GUIDELINES FOR ADMINISTRATION OF INJECTABLE ARTESUNATE FOR SEVERE MALARIA

WHO RECOMMENDED TREATMENT [2]

Artesunate powder 60mg + Bicarbonate ampoule + Saline solution *

PRODUCT DESCRIPTION [1]

Dose: For children < 20 kg: 3.0 mg/kg
For children > 20 kg and adults: 2.4 mg/kg

Can be given by intravenous route (IV) or intramuscular route (IM).
IV is the preferred route of administration.
Please refer to the patient information leaflet for more information.

*** Water for injection is not an appropriate dilutant**

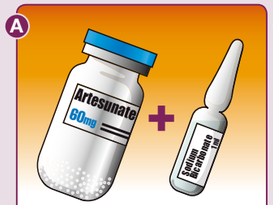
1 WEIGH THE PATIENT

2 DETERMINE THE NUMBER OF VIALS NEEDED

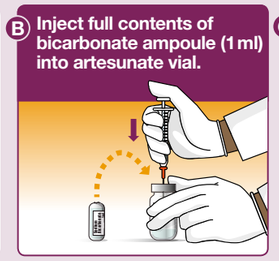
Weight	less than 25 kg	26-50 kg	51-75 kg	76-100 kg
60 mg vial	1	2	3	4

3 RECONSTITUTE

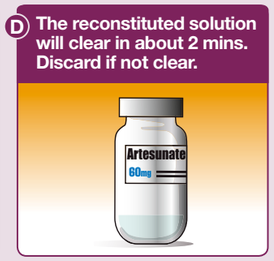
- Activate the drug: artesunate powder + bicarbonate ampoule (immediately before use)

A 

Artesunate powder + bicarbonate ampoule

B Inject full contents of bicarbonate ampoule (1 ml) into artesunate vial.


C Shake until dissolved. Solution will be cloudy.


D The reconstituted solution will clear in about 2 mins. Discard if not clear.


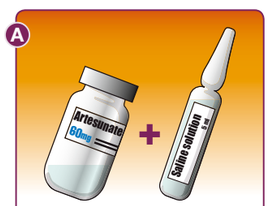
4 DILUTE

- Reconstituted artesunate + saline solution (or dextrose 5%)
- Volume for dilution

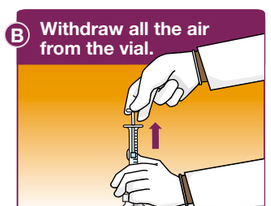
	IV	IM
Bicarbonate solution volume	1 ml	1 ml
Saline solution volume	5 ml	2 ml
Total volume	**6 ml**	**3 ml**
Artesunate 60 mg solution concentration	10 mg/ml	20 mg/ml

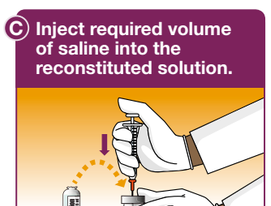
IMPORTANT

Water for injection is not an appropriate dilutant

A 

Artesunate reconstituted + saline solution

B Withdraw all the air from the vial.


C Inject required volume of saline into the reconstituted solution.


D Artesunate solution is now ready for use.


1. World Health Organization (WHO) List of Prequalified Medicinal Products (http://apps.who.int/prequal/query/ProductRegistry.aspx?list=ma): artesunate injectable, reference N° MA051, prequalified on 05-Nov-2010.
2. World Health Organization, Management of Severe Malaria - A practical handbook - Third edition - April 2013 - (http://www.who.int/malaria/publications/atoz/9789241548526/en/index.html)

5 CALCULATE THE DOSE

- Calculate and withdraw the required dose **in ml** according to route of administration:

Less than 20 kg

For intravenous route (IV)	For intramuscular route (IM)
Concentration: 10 mg/ml	**Concentration: 20 mg/ml**
3.0 mg x body weight (kg) / IV artesunate solution concentration 10 mg/ml	3.0 mg x body weight (kg) / IM artesunate solution concentration 20 mg/ml
Round up to the next whole number	Round up to the next whole number
Example:	**Example:**
Dose needed (ml) for 8 kg child: $\frac{3.0 \times 8}{10}$ = 2.4 ml	Dose needed (ml) for 8 kg child: $\frac{3.0 \times 8}{20}$ = 1.2 ml
2.4 ml rounded up to **3 ml**	1.2 ml rounded up to **2 ml**

Weight kg	Dose mg	Dose ml
6 - 7	20	2
8 - 10	30	3
11 - 13	40	4
14 - 16	50	5
17 - 20	60	6

Weight kg	Dose mg	Dose ml
6 - 7	20	1
8 - 10	30	2
11 - 13	40	2
14 - 16	50	3
17 - 20	60	3

More than 20 kg

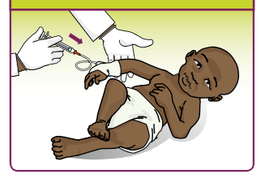
Concentration: 10 mg/ml	Concentration: 20 mg/ml
2.4 mg x body weight (kg) / IV artesunate solution concentration 10 mg/ml	2.4 mg x body weight (kg) / IM artesunate solution concentration 20 mg/ml
Round up to the next whole number	Round up to the next whole number
Example:	**Example:**
Dose needed (ml) for 26 kg child: $\frac{2.4 \times 26}{10}$ = 6.24 ml	Dose needed (ml) for 26 kg child: $\frac{2.4 \times 26}{20}$ = 3.12 ml
6.24 ml rounded up to **7 ml**	3.12 ml rounded up to **4 ml**

Weight kg	Dose mg	Dose ml
20 - 25	60	6
26 - 29	70	7
30 - 33	80	8
34 - 37	90	9
38 - 41	100	10
42 - 45	110	11
46 - 50	120	12
51 - 54	130	13
55 - 58	140	14
59 - 62	150	15
63 - 66	160	16
67 - 70	170	17
71 - 75	180	18
76 - 79	190	19
80 - 83	200	20
84 - 87	210	21
88 - 91	220	22
92 - 95	230	23
96 - 100	240	24

Weight kg	Dose mg	Dose ml
20 - 25	60	3
26 - 29	70	4
30 - 33	80	4
34 - 37	90	5
38 - 41	100	5
42 - 45	110	6
46 - 50	120	6
51 - 54	130	7
55 - 58	140	7
59 - 62	150	8
63 - 66	160	8
67 - 70	170	9
71 - 75	180	9
76 - 79	190	10
80 - 83	200	10
84 - 87	210	11
88 - 91	220	11
92 - 95	230	12
96 - 100	240	12

Remark: the upper limit for each weight band is 0.9 kg e.g. 14 - 16 kg covers 14 - 16.9 kg.

6 ADMINISTER

IV: slow bolus 3-4 ml per minute.


IM: Inject slowly. Spread the doses of more than 2 ml over different sites for babies and 5 ml for adults.


7 DOSING SCHEDULE

1. Give **3 parenteral doses** over 24 hours as indicated in the opposite table

2. Give **parenteral doses** for a minimum of 24 hours once started irrespective of the patients ability to tolerate oral treatment earlier.

- **Day 1** **Dose 1: on admission (0 Hours)**
  Dose 2: 12 hours later
- **Day 2** **Dose 3: 24 hours after first dose**

- When the patient can take oral medication, prescribe a full 3-day course of recommended first line oral Artemisinin Combination Therapy (ACT).
  The first dose of ACT should be taken **between 8 and 12 hours** after the last injection of artesunate.
- Until the patient is able to take oral medication, continue parenteral treatment (one dose a day) **for a maximum of 7 days**.
- A course of injectable artesunate should always be followed by a 3-day course of ACT.

- Evaluate the patient's progress regularly.

IMPORTANT

- **Prepare a fresh solution for each administration.**
- **Discard any unused solution after use.**

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