

Roll Back Malaria (RBM) Malaria in Pregnancy (MIP) Working Group Meeting

Maputo, Mozambique

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Global **Malaria** Programme



World Health
Organization

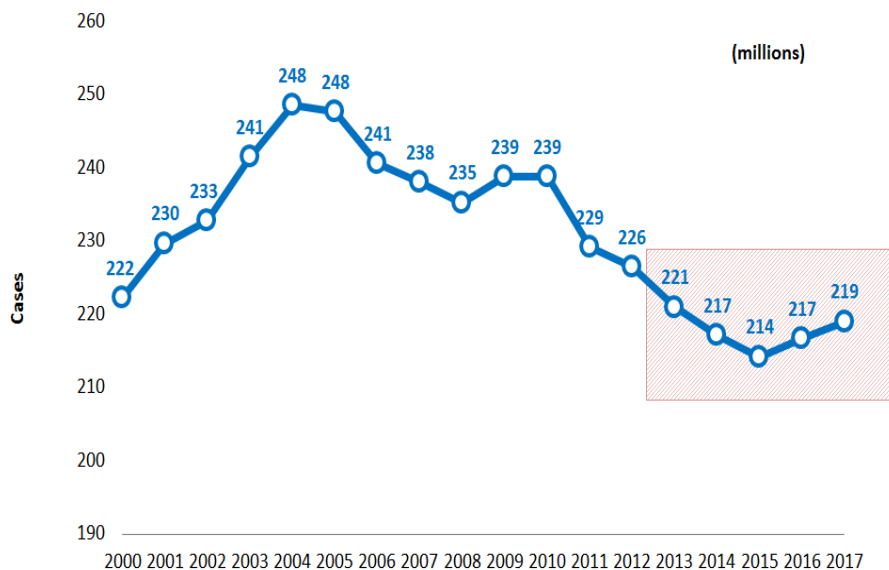


Outline

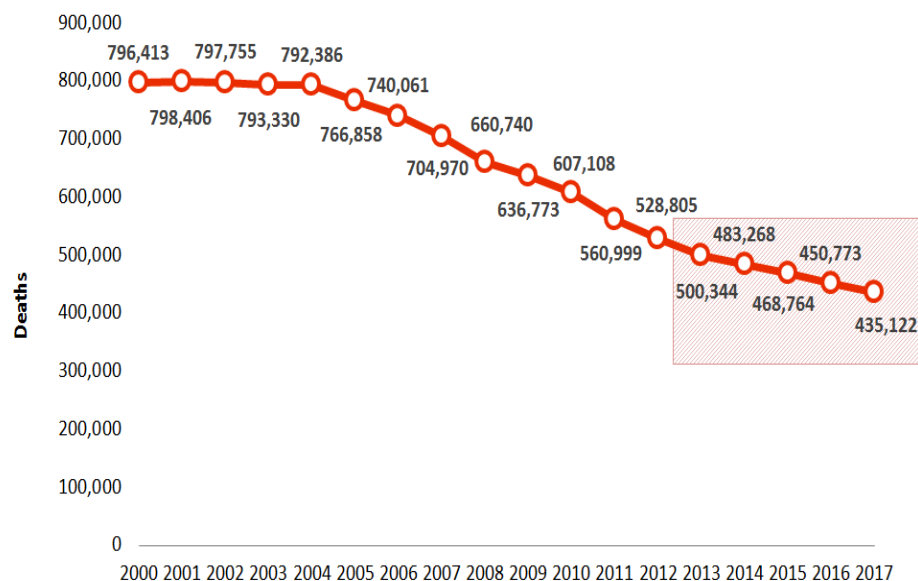
- ❑ World Malaria Report 2018
- ❑ Update of guidelines
- ❑ Quality-assured SP
- ❑ WHO Essential Medicines List



Number of malaria cases worldwide, 2000–2017



Number of malaria deaths worldwide, 2000–2017



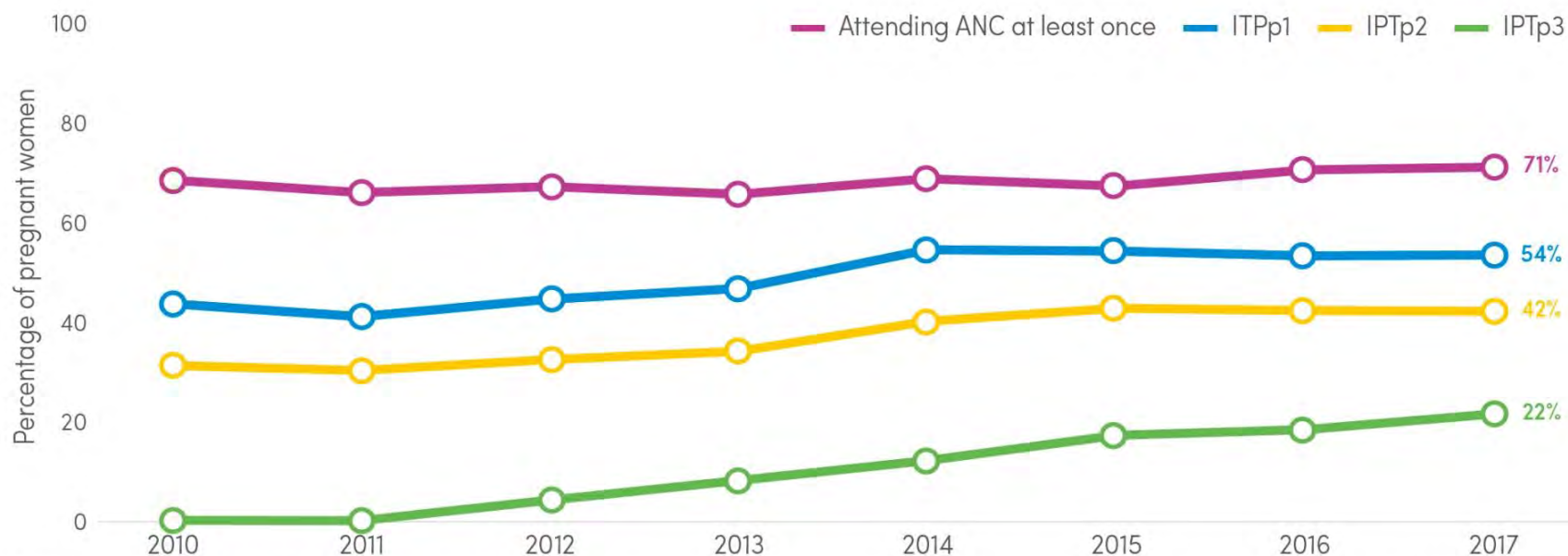
Full report: <https://www.who.int/malaria/publications/world-malaria-report-2018/report/en/>



Pregnant women protected by IPTp (Sub-Saharan Africa), 2010–17

FIG. 3.5.

Percentage of pregnant women attending ANC at least once and receiving IPTp, by dose, sub-Saharan Africa, 2010–2017 *Source: NMP reports, WHO and US Centers for Disease Control and Prevention (CDC) estimates.*



ANC: antenatal care; IPTp: intermittent preventive treatment in pregnancy; NMP: national malaria programme; WHO: World Health Organization.

Data received from 35 countries for IPTp-1 and IPTp-2, and from 33 countries for IPTp-3

2016 WHO ANC guidelines

Increased number of opportunities to receive IPTp-SP



| ANC Contact Schedule and Proposed Time of IPTp-SP Administration <i>(To be adapted to country context, also considering disease burden and health needs)</i> | | MiP-related Interventions and Considerations during ANC Contacts |
|---|--|--|
| Contact 1: Up to 12 weeks | | <ul style="list-style-type: none"> Register pregnant women, provide ITNs, and counsel on their use. Screen for HIV. Administer 30 to 60 mg of elemental iron and 400 µg (0.4 mg) of folic acid. Counsel to return for a visit at 13 to 16 weeks (see contact 1a below) to receive the first dose of IPTp-SP (as directed by national guidelines).* Counsel on prompt diagnosis and effective treatment/malaria case management during pregnancy. |
| Additional contact (1a): <i>In moderate to high malaria transmission areas in Africa where IPTp-SP is policy, a contact should be made early in the second trimester (13 to 16 weeks) to administer SP as early as possible.</i> | IPTp-SP dose 1 | <p>Remember:</p> <ul style="list-style-type: none"> Do not administer IPTp-SP before week 13 of pregnancy. Administer the first IPTp-SP dose as early as possible in the second trimester to fully benefit from the protective capacity in this critical period of pregnancy.† Administer the second dose of IPTp-SP one month later. |
| Contact 2: 20 weeks | IPTp-SP dose 2 | <ul style="list-style-type: none"> Administer the following doses of IPTp-SP starting from the scheduled contact at 20 weeks, observing at least one-month intervals between SP doses. SP can be safely administered from the beginning of the second trimester until the time of delivery. One full dose of IPTp-SP consists of 1,500 mg/75 mg SP (i.e., three tablets of 500 mg/25 mg SP). Provide IPTp-SP by directly observed treatment. Pregnant women on co-trimoxazole should not receive IPTp-SP due to an increased risk of adverse events when both drugs are given in parallel. Continue to administer 30 to 60 mg of elemental iron and 400 mcg (0.4 mg) of folic acid. Continue counseling as above. |
| Contact 3: 26 weeks | IPTp-SP dose 3 | |
| Contact 4: 30 weeks | IPTp-SP dose 4 | |
| Contact 5: 34 weeks | IPTp-SP dose 5 | |
| Contact 6: 36 weeks | No SP administration if last dose was received at contact 5 in week 34 | |
| Contact 7: 38 weeks | IPTp-SP dose 6 (if no dose was received at contact 6 in week 36) | |
| Contact 8: 40 weeks | | |
| Pregnant women should receive MiP interventions as appropriate, even when they come at weeks not designated in the contact schedule. | | |
| Despite the known side effects associated with sulfonamides, SP for intermittent preventive treatment in pregnancy is generally very well tolerated. Mild and transient side effects including nausea, vomiting, weakness and dizziness have been reported by some women, particularly with the first dose of SP. Studies have demonstrated that side effects tend to decrease with the administration of further doses (§±). Side effects should be discussed openly and managed in the ANC. | | |



Current recommendations to treat Pf malaria (MTG, 3rd ed 2015)

- ❑ **1st trimester:** 7 days of quinine + clindamycin
Only use an ACT if quinine not available or adherence to 7 day treatment not guaranteed
- ❑ **2nd and 3rd trimesters:** ACT effective in the region
- ❑ Primaquine is **contra-indicated** in pregnancy both for transmission reduction (anti-gametocyte) in falciparum infections and anti-relapse treatment in vivax or ovale infections



Review plans

- ❑ Recent data available on exposure to **ACTs in the 1st trimester of pregnancy**: Stephanie Dellicour et al: First-trimester artemisinin-based combination treatments and the risk of adverse pregnancy outcomes in a meta-analysis of observational studies. (PLOS Medicine | <https://doi.org/10.1371/journal.pmed.1002290> May 2, 2017)
- ❑ The **GRADE** and evidence to inform the 2015 WHO recommendation on pregnancy in the MTG is presently being updated by the WHO Infectious Disease Group.
- ❑ The WHO **Therapy Technical Expert Group** is scheduled for **September 2017**, to review the updated evidence and provide revised recommendations on the use of artemisinin derivatives in the 1st trimester of pregnancy.

Update

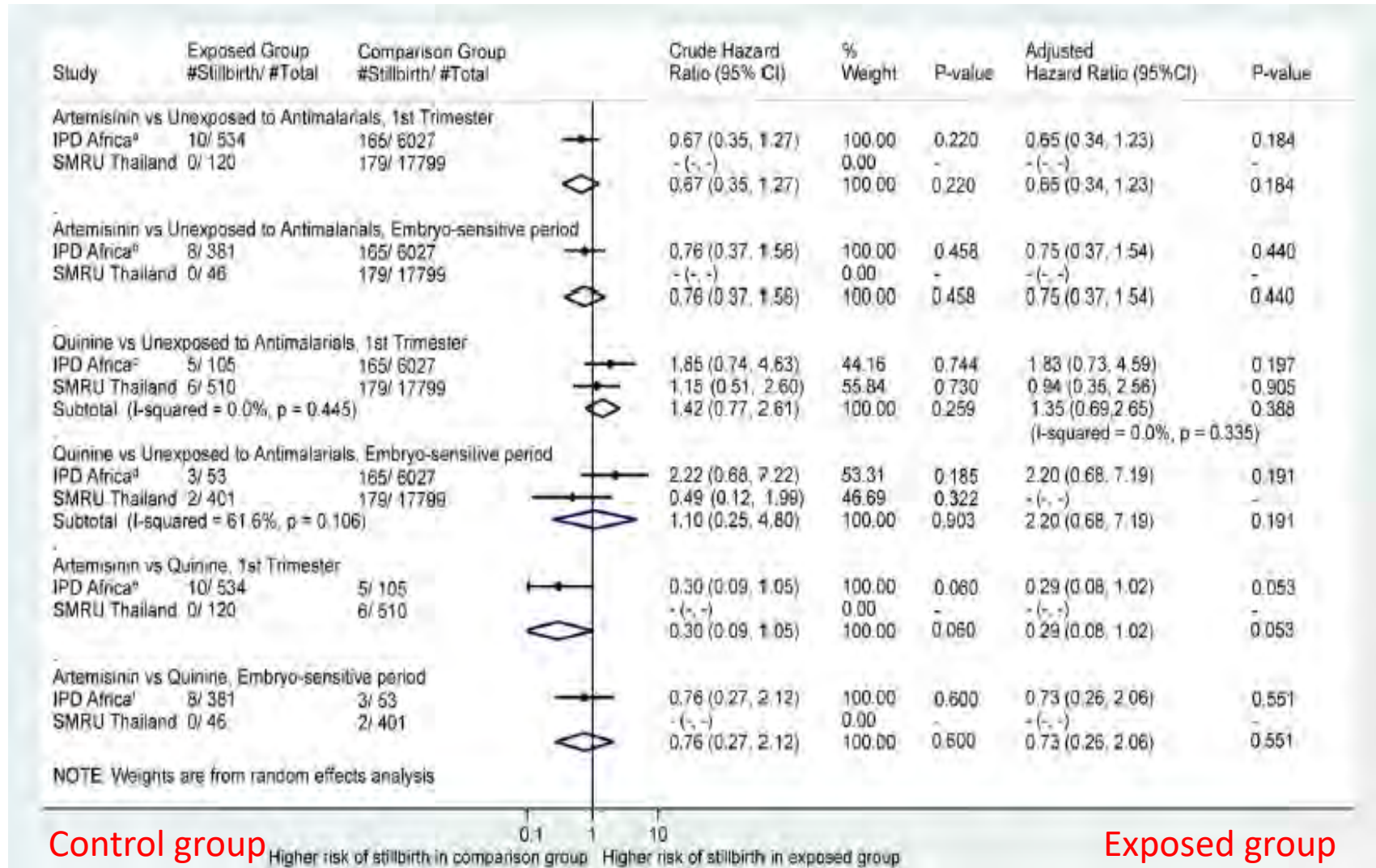


- ❑ December 2017: The WHO Technical Expert Group on Malaria Chemotherapy, as Guidelines Development Group generated the following recommendation:

*"Artemisinin combination treatments should be used to treat malaria in pregnant women in the first trimester of pregnancy except where the partner **drug is contraindicated as with AS+SP.**"*

- ❑ The recommendation was endorsed by MPAC in July 2018 and the release of these new recommendations is pending internal agreement with WHO LEG and PUB on the disclaimer to be added to all **WHO guidelines and publications which recommend "off-label use" of medicines.**

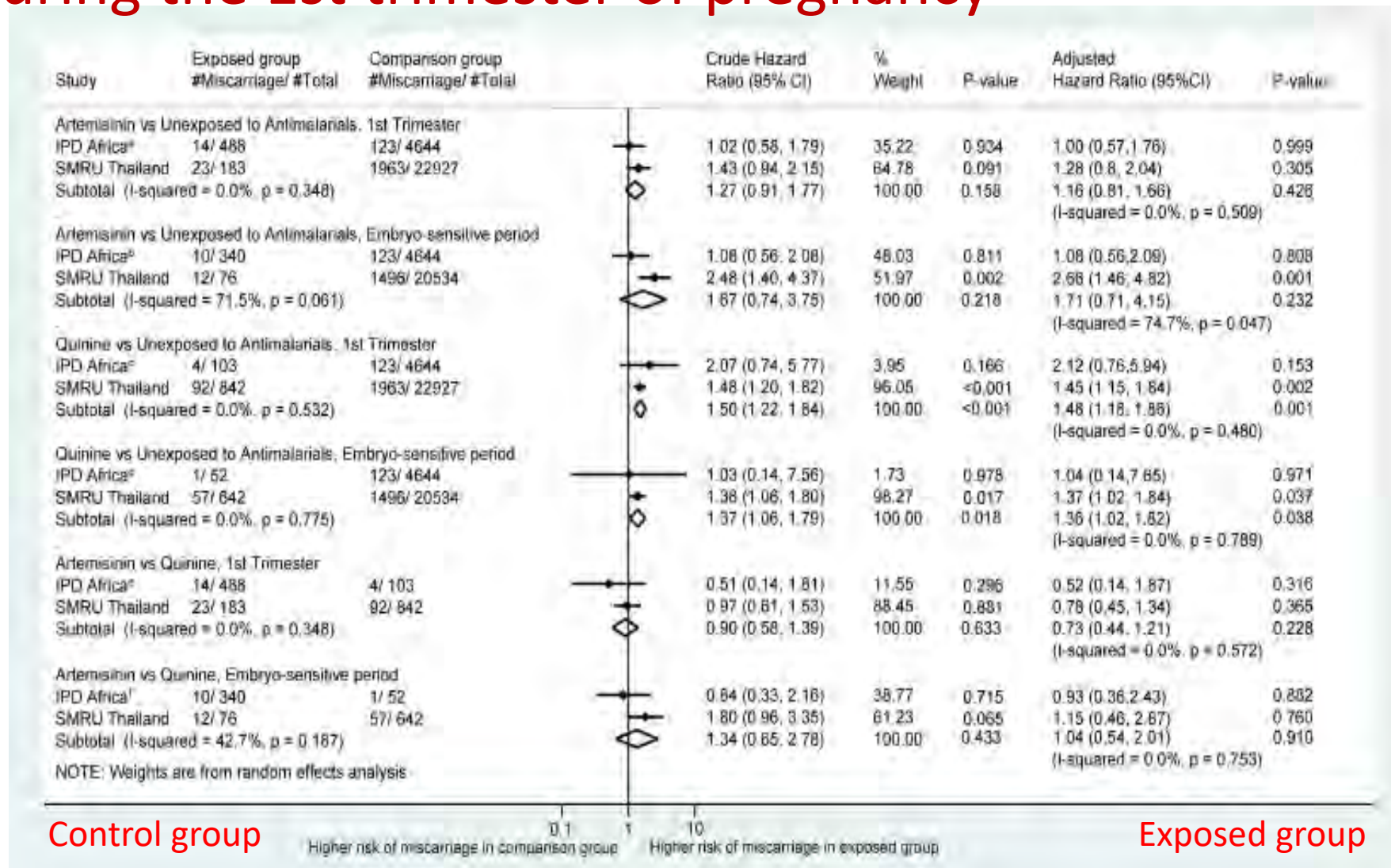
Stillbirth and exposure to quinine and artemisinins during the 1st trimester of pregnancy



Miscarriage and exposure to quinine and artemisinins



during the 1st trimester of pregnancy



Control group

Exposed group

Treatment with quinine + clindamycin



7 days of quinine (10 mg salt/kg bw, three times a day)
plus clindamycin (10mg/kg, two times a day)

- ❑ With quinine sulfate 300 mg tablets and clindamycin 300mg capsules, a pregnant women of 60 kg bw needs to take 2 tablets of quinine three times a day for seven days (= 42 tablets) plus two capsules of clindamycin twice a day for seven days (= 28 capsules) at different times of the day.
- ❑ This regimen and the side effects of quinine explain the poor adherence to treatment and, for this reason, pregnant women do not receive an effective treatment for malaria.
- ❑ In reality, clindamycin is often not available and the different formulations and strengths of quinine tablets on the market, make even more difficult to adhere to the above recommendations for malaria treatment in pregnancy.





Pregnant women are a high risk group

Acquired Immunity = Low

Clinical Illness

Severe Disease

Risk to Mother

- Death following severe malaria

Risk to Fetus

- Prematurity
- Miscarriage
- Stillbirth

- All pregnancies at risk
- Up to 60% fetal loss and 10% maternal deaths
- 50% maternal mortality with severe disease



Quality-assured sulfadoxine-pyrimethamine



WHO Prequalification (last updated 1 Feb 2019):

<https://extranet.who.int/prequal/content/prequalified-lists/medicines>

Displaying: 1 - 50 of 58

[Download List](#)

| WHO Reference Number | International nonproprietary name (INN) | Therapeutic Area | Applicant | Dosage form & strength | Date of prequalification |
|----------------------|---|------------------|--|---|--------------------------|
| MA068 | Pyrimethamine/Sulfadoxine + Artesunate | Malaria | Guilin Pharmaceutical Co Ltd, No 43 Qilidian Road, Guilin, Guangxi, 541 004, China (People's Republic of) | Tablets + Tablets 25mg/500mg + 100mg | 18 Dec 2018 |
| MA135 | Artesunate + Sodium Bicarbonate + Sodium Chloride | Malaria | Ipca Laboratories Ltd, 48 Kandivli Industrial Estate, Kandivli (West), Mumbai, Maharashtra, 400 067, India | Powder, solvent and diluent for solution for injection 60mg + 5%w/v + 0.9%w/v | 18 Dec 2018 |
| MA113 | Pyrimethamine/Sulfadoxine | Malaria | Guilin Pharmaceutical Co Ltd, No 43 Qilidian Road, Guilin, Guangxi, 541 004, China (People's Republic of) | Tablet 25mg/500mg | 31 Oct 2018 |
| MA132 | Amodiaquine (hydrochloride)/Artesunate | Malaria | Micro Labs Ltd, 27 Race Course Road, Bangalore, Karnataka, 560 001, India | Tablet 67.5mg/25mg | 31 Oct 2018 |

First WHO-prequalified SP available since Oct 2018

Second source on Global Fund List of Malaria Pharmaceutical Products (last updated 25 Jan 2019):

https://www.theglobalfund.org/media/4756/psm_products_malaria_list_en.pdf

| | | | | | | | | | | |
|----|-----------------------------|--------------|------------|------------------------|---|-------|--|--------|-----------------------------|---|
| | Sulfadoxine+Pyrimethamine | 500mg+25mg | Tablet FDC | Guilin Pharmaceuticals | A | MA113 | Guilin Pharmaceuticals Co. Ltd, No. 43 Quilidian road, | China | HDPE bottle; Blister | 100's, 1000's 3', 3x50, 3x100 |
| 29 | Sulfadoxine + Pyrimethamine | 500mg + 25mg | Tablet | Remedica | B | Yes | Limassol | Cyprus | Al/PVC blister PE container | 1*3 tabs and , 10* 3tabs 100's and 1000's |

End of A or B products list



WHO Model List of Essential Medicines

20th List
(March 2017)
(Amended August 2017)

Status of this document

This is a reprint of the text on the WHO Medicines website

<http://www.who.int/medicines/publications/essentialmedicines/en/>

WHO Model List of Essential Medicines: Inclusion of SP for IPTp

- Dossier prepared and submitted in December 2018
- WHO Expert Committee meeting, Geneva, 1-5 April 2019

(http://www.who.int/selection_medicines/committees/en/)



**Thank you very much
for your attention**