Folic acid supplementation under antifolate antimalarial regimens

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The importance of anaemia

- Global anemia prevalence in 2010 was 32.9%
  - It accounts for 8.8% of years lived with disability
- In sub-Saharan Africa anaemia is among the **principal causes of mortality and morbidity**
- It is estimated that about 468 million women aged 15-49 years worldwide are anaemic and nearly half of them live in Africa
- Anaemia is an **important health indicator** for women of reproductive age
- In low income settings, its etiology is often multifactorial
  - poor nutrition, infections, menstruation, pregnancy, others

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Folic acid supplementation

- The WHO recommends the intake of iron and **folic acid** for anaemia
- **Folic acid supplementation is questioned** in contexts of malaria endemicity due to its role on the pharmacological action of antifolate antimalarial drugs
- *In vitro* studies and clinical trials have shown that folate supplementation **may reduce the efficacy** of antifolate antimalarial regimens

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Use of antimalarial antifolates

- **Sulfadoxine-pyrimethamine** (**SP**) is an antifolate antimalarial drug widely used for malaria prevention (IPTp and SMC)
- **Trimetropim plus sulfametoxazole- Cotrimoxazole (CTX)** is another antifolate drug with antimalarial effect and widely used to prevent opportunistic infections in HIV-infected patients
    - inhibit the folate *de novo* pathway of malaria parasites leading to parasite death
    - parasite development of resistance
- Folic acid is recommended to prevent and treat anemia during pregnancy and to anemic children exposed to malaria

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Current guidelines and recommendations

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The WHO recommends SP as **intermittent preventive treatment of pregnancy** (IPTp):

Where malaria transmission is moderate to high	Give at least three SP tablets each containing 500mg of sulfadoxine and 25mg of pyrimethamine.
Where malaria transmission has been reduced but where there are no data to determine whether to stop IPTp-SP	Use same regimen as above.
Mode of administration	IPTp-SP should be given as directly observed therapy at each antenatal visit, starting as early as possible in the second trimester until the time of delivery, with each dose given at least one month apart. **IPTp-SP should not be given to women on cotrimoxazole because of a higher risk of adverse events.**

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Intermittent preventive treatment in infants (IPTi) with SP is recommended in SSA:

Where malaria transmission is moderate to high and where parasite resistance to SP is not high, defined as a prevalence of the *Pfdhps* 540 mutation of ≤ 50%	Give a full therapeutic course of SP delivered through the Expanded Programme on Immunization (EPI).
Mode of administration	Give the therapy at intervals corresponding to routine vaccination schedules for the second and third doses of diphtheria, tetanus and pertussis (DTP) and measles vaccination — usually at 8-10 weeks, 12-14 weeks, and ~9 months of age. **Intermittent preventive treatment in infants (IPTi) should not be given to infants in a sulfa-based medication (as cotrimoxazole) because of a higher risk of adverse events.**

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SP is recommended for children aged 3-59 months living in the Sahel region as **seasonal malaria chemoprotection** (SMC):

Where malaria transmission and the majority of clinical malaria cases occur during a short period of about four months, the clinical attack rate of malaria is greater than 0.1 attack per transmission season in the target age group, and AQ+SP remains efficacious (>90% efficacy)	Give a complete treatment course of amodiaquine plus sulfadoxine-pyrimethamine (AQ+SP) to children aged between 3 and 59 months at monthly intervals, beginning at the start of the transmission season, to a maximum of four doses during the malaria transmission season.
Mode of administration	• Infants < 12 months old: AQ – half of a 153mg tablet given once daily for three days and a single dose of SP - half of a 500/25mg tablet. • Children 12 – 59 months: AQ – a full tablet of 153 mg given once daily for three days and a single dose of SP - a full tablet of 500/25mg. The single dose of SP is given only on the first day together with the 1st dose of AQ. **Seasonal malaria chemoprotection (SMC) should not be given to children in a sulfa-based medication (as cotrimoxazole) because of a higher risk of adverse events.**

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Malaria treatment

One of the artemisinin-based combination therapies (ACT) recommended to treat uncomplicated malaria is **artesunate + SP**.

Target dose:

- Artesunate: 4 mg/kg of body weight per day during 3 days
- **SP:** a single administration of at least 25/1.25 mg/kg of body weight on day 1.
- There is no fixed dose combination.

The official WHO guidelines discourage the artesunate + SP combined therapy in areas of SP resistance.

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Folic acid supplementation recommendations

The WHO recommendations for **pregnant women** to prevent anaemia in pregnancy, puerperal sepsis, low birth weight and preterm birth are:

Where anaemia prevalence in pregnancy is less than 40%	Give 30-60 mg of elemental iron and **0.4 mg** of folic acid.
Where anaemia prevalence in pregnancy is 40% or more	Give 60 mg of elemental iron and **0.4 mg** of folic acid.
Mode of delivery	Give daily starting as early as possible in pregnancy and continuing throughout pregnancy.
Where anaemia prevalence is less than 20% (with an accurate measurement of maternal blood Hb concentrations) or in case of side-effects of daily iron	*Give intermittent oral iron and folic acid supplementation with 120 mg of elemental iron and 1.8 mg of folic acid once weekly.*

Also for **postpartum women**, the WHO recommends oral iron supplementation, either alone or in combination with folic acid for 6-12 weeks after delivery in settings where gestational anaemia is of public health concern (prevalence >20%).

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For the treatment of **iron deficiency anaemia**, the WHO recommends:

>2 years	25 mg iron, **0.1-0.4 mg** folic acid
2-12 years	60 mg iron, **0.1-0.4 mg** folic acid
Adolescents and adults	120 mg iron, **0.1-0.4 mg** folic acid
Pregnant women	120 mg iron, **0.1-0.4 mg** folic acid
Duration	Three months

For **infants** and **young children**:

A 2006 WHO consultation on prevention and control of iron deficiency in infants and young children in malaria endemic areas **did not support supplemental folic acid** in this population.

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The WHO recommends a low dose of folic acid (**0.4 mg daily**) because it does not reduces SP efficacy

Higher doses of folic acid (**5 mg daily**) significantly reduce SP efficacy and should not be given at the same time.

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Challenges

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Current situation

- Folic acid supplements are **commonly available in 5 mg formulations** in many international settings
- The WHO Model Essential Medicines List (EML), categorizes folic acid as an anti-anaemia medicine, with listed dosages for folic acid alone in **1 mg and 5 mg tablets**
- Folic acid is also available in **0.4 mg tablets in combined iron-folic acid supplements** and alone only for peri-conceptual use for prevention of neural tube defects

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- There is a need to **increase availability** of **lower-dose folic acid** supplements in endemic malaria countries for anemia prevention in pregnant women and other groups receiving antifolates and exposed to malaria

- Evidence needed on folic acid status in population groups besides pregnant women, receiving CTXp and being exposed to malaria

Thank you!

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