Proposal for an Evidence Review Group on intermittent screening and treatment and safety of artemisinin in pregnancy

February 2015, Geneva, Switzerland

Introduction

Malaria in pregnancy contributes significantly to maternal and neonatal mortality. Intermittent preventive treatment against malaria in pregnancy (IPTp) is a highly cost-effective intervention that significantly improves the health of mothers and their newborns in areas of moderate to high malaria transmission. In October 2012, on the advice of the Malaria Policy Advisory Committee (MPAC) and the work of a dedicated evidence review group (ERG), WHO updated the policy for IPTp with sulphadoxine-pyrimethamine (IPTp-SP). The new policy recommends that women who live in areas of moderate to high malaria transmission should receive IPTp-SP as early as possible in the second trimester, and at each scheduled antenatal care (ANC) visit thereafter, with SP doses given at least 1 month apart.

Since the updated IPTp policy was released, several countries throughout sub-Saharan Africa plan to update their country policies in line with the new recommendations, but IPTp implementation still remains low. In 2013, the coverage of IPTp with two doses of SP was 43% (among 31 reporting countries) – well below national and international targets, and only 17% of all pregnant women received three or more doses of IPTp (among nine reporting countries), in line with the latest WHO recommendations. It is of particular concern that, according to some preliminary estimates for 2014, coverage may be declining in some countries.

Background

To respond to concerns about the effectiveness of IPTp-SP in areas with *Plasmodium falciparum* antifolate resistance or decreasing malaria transmission, and to evaluate the role of potential alternatives to IPTp-SP, WHO convened a second ERG meeting on IPTp in July 2013. MPAC considered the outcome of that ERG meeting at the committee’s fourth meeting in September 2013 and recognized that, in a small number of discrete areas in eastern and southern Africa, resistance of *P. falciparum* to SP has reached levels at which IPTp-SP may no longer be effective in preventing low birth weight. These are areas where *P. falciparum* parasites carry sextuple resistance mutations in dhfr and dhps genes, including the A581G dhps mutation. MPAC also noted that, in many areas with high prevalence of parasites with quintuple antifolate mutations,
IPTp-SP still confers some benefit in terms of pregnancy outcomes. On balance, MPAC concluded that there is currently insufficient data to determine at what level of SP resistance IPTp-SP should be discontinued in the absence of an established and effective alternative. MPAC also concluded that there are currently insufficient data to define the level of Plasmodium falciparum transmission at which IPTp-SP may cease to be cost-effective from a public health point of view.

At the same session, the potential role of mefloquine use for IPTp (IPTp-MQ) was reviewed, based on the results of multicentre clinical trials using mefloquine for IPTp, at 15 mg/kg as a single or split dose. The trials compared mefloquine to SP in HIV-negative pregnant women, and the benefits of three monthly doses of IPTp-MQ added to daily co-trimoxazole (CTX) prophylaxis in HIV-infected pregnant women. Based on the evidence review, the MPAC agreed that MQ 15 mg/kg (single or split dose regimen) should not be recommended for IPTp given a high frequency of adverse events related to poor tolerability.

New evidence

During the past 2 years, several studies have been completed that have evaluated the efficacy, safety, feasibility, acceptability and cost-effectiveness of an alternative intervention to prevent the consequences of malaria in pregnancy, including intermittent screening and treatment of malaria in pregnancy (ISTp). This intervention uses rapid diagnostic tests (RDTs) for screening of pregnant women with treatment of RDT positive women with an effective antimalarial combination. The antimalarial studies included SP, dihydroartemisinin + piperaquine (DP), and artemether + lumefantrine (AL). In addition, meta-analyses have been completed to evaluate 1) the impact of anti-folate resistance and level of malaria transmission on the effectiveness of IPTp-SP; and 2) the comparative effectiveness of IPTp-SP with ISTp-AL and ISTp-DP in areas with different levels of SP resistance and malaria transmission intensity.

Moreover, during recent years, a growing body of evidence has been accumulated that contributes to an understanding of the clinical safety of the artemisinin derivatives in the first trimester of pregnancy, and of the efficacy of different artemisinin-based combination therapies in treatment of malaria in pregnancy. A series of safety studies have been completed to assess pregnancy outcomes of women with malaria exposed to different artemisinin derivatives or to quinine during the first trimester of pregnancy, compared to pregnant women not exposed to either malaria or antimalarial treatment.

Proposal

To review the new evidence described above, the WHO/Global Malaria Programme (GMP) is proposing to hold a meeting of an ERG for Malaria in Pregnancy (ERG-MiP), focusing on the effectiveness of ISTp compared with IPTp in areas with SP resistance and reduced malaria transmission, and the safety of antimalarials in pregnancy. The ERG will convene for 4 days in July 2015, and will be held in two parts: part 1 will focus on assessing the evidence for ISTp, while the second part 2 will focus on assessing the evidence for efficacy and safety of antimalarials in pregnancy. Each part will enlist the participation of a different group of scientists with relevant expertise.

Requested action by the MPAC

Provide advice to GMP on proposed plan for the review and selected studies.

Annex

List of manuscripts proposed for the WHO MiP-ERG, 13–16 July 2015.