

# Time for new recommendations on cotrimoxazole prophylaxis for HIV-exposed infants in developing countries?

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## Background

*Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii*) pneumonia has been reported to be a leading cause of death in HIV-infected infants. In 2000 the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) issued recommendations on the use of cotrimoxazole (trimethoprim-sulfamethoxazole), as prophylaxis against *Pneumocystis jirovecii* for HIV-exposed infants. Cotrimoxazole is a broad-spectrum antimicrobial agent used to target a range of bacteria as well as some fungi and protozoa.

These recommendations on cotrimoxazole prophylaxis emerged shortly after studies in Abidjan, Côte d'Ivoire, showed its impact on reducing morbidity in HIV-infected adults. However, the evidence of benefit in children was much weaker and consisted of positive impact in observational studies from the United States of America; an ecological study from Thailand that ascribed a decline in hospitalization cases of *Pneumocystis jirovecii* to an increased use of cotrimoxazole; and conflicting evidence from retrospective analyses of hospital data from three African studies.<sup>1</sup>

Diagnosis of HIV in children aged less than 12 months is difficult as it requires the use of costly molecular diagnostics. Since it is not always possible to know which HIV-exposed infants are infected, the guidelines recommended that all HIV-exposed children should receive cotrimoxazole prophylaxis.

## More evidence

Since the 2000 guidelines were published, further evidence on the effectiveness of cotrimoxazole prophylaxis against opportunistic infections in HIV-infected children emerged from the CHAP study, a randomized, placebo-controlled trial of cotrimoxazole in Zambia.<sup>2</sup> The study, which showed a significant impact on reducing mortality, included only HIV-infected children from 6 months to 14 years of age. Of note is that

only 3% of the cohort was aged less than 12 months and the majority were symptomatic and had a CD4+ lymphocyte % < 20%. Following the publication of the CHAP study, WHO/UNAIDS/United Nations Children's Fund (UNICEF) published a statement reinforcing recommendations on the use of cotrimoxazole prophylaxis for HIV-infected as well as HIV-exposed children.<sup>3</sup> This statement was followed in 2006 by WHO guidelines on cotrimoxazole prophylaxis for HIV-related infections. They reinforced earlier guidelines and recommended it for HIV-exposed breastfed children until HIV was excluded or at least 6 weeks after complete cessation of breastfeeding.

## New data

While we reaffirm the importance of cotrimoxazole prophylaxis for HIV-infected children we believe, that with the emergence of new data, especially around the use of antiretroviral prophylaxis during breastfeeding, the time has come to revisit the guidelines for HIV-exposed infants. Our reasoning for this is described here.

## Fewer HIV-infected infants

The original call for cotrimoxazole prophylaxis was made on the assumption that some 20% of infants could be infected during the ante- and intra-partum period and that a further 15% of infants could be infected through breastfeeding. However, if the proportion of infants who are infected is lower, the benefits of mass prophylaxis may not supersede the risks. Even with interventions for prevention of mother-to-child transmission using single dose nevirapine, Gill et al. in a modelling exercise showed that, as the proportion of HIV-infected infants declined, the benefits of mass prophylaxis on a population level are probably superseded by the risks.<sup>1</sup> Although developing countries still face enormous challenges in increasing coverage of services for prevention of mother-to-child transmission (estimated by UNAIDS

to be only 45%), we are now on the brink of a new era with much greater potential for lower proportions of HIV-infected infants. New WHO guidelines call for pregnant women with CD4 count  $\leq$  350 to receive highly active antiretroviral therapy (HAART) and those with counts  $>$  350 to receive zidovudine from week 28 with single dose nevirapine during labour. With these interventions, it is likely that less than 2% of infants of HIV infected mothers will be born infected. Furthermore, following considerable evidence from studies in developing countries,<sup>4</sup> WHO is now recommending that breastfeeding women receive HAART or the infants receive nevirapine prophylaxis (the latter is probably the option that will be taken by most developing countries). With this strategy, again, only 1–2% of infants are likely to be infected. Therefore we would be providing prophylaxis for a very small proportion of children who are likely to be infected (about 5%) and exposing about 95% of the infants who are uninfected to unnecessary risks associated with antibiotic treatment.

## Lack of evidence

Apart from the potential benefit of cotrimoxazole in preventing malaria in HIV-negative infants, there are no clinical trials testing its effect in HIV-negative infants and thus no definitive evidence showing benefit. In fact, a study in South Africa showed an increased risk for diarrhoea in HIV-negative infants who received cotrimoxazole prophylaxis.<sup>5</sup>

## Side-effects

In addition to lack of evidence of benefit in HIV-negative children, there is a problem of unnecessarily exposing HIV-negative infants to the well known side-effects of cotrimoxazole. These range from skin reactions and gastrointestinal disturbances to marrow suppression which could lead to neutropenia and anaemia. Although most adverse effects are mild, there are some rare cases of Stevens-Johnson syndrome.<sup>6</sup>

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(Submitted: 25 January 2010 – Revised version received: 17 March 2010 – Accepted: 29 March 2010)

Furthermore, once the new guidelines on prevention of breastfeeding transmission are implemented, breastfeeding infants are likely to be receiving daily doses of nevirapine as well as cotrimoxazole. Since both drugs are known to cause neutropenia, there is a risk of additive adverse effects.

### Potential resistance

Cotrimoxazole has antimicrobial activity against a wide range of pathogens and its routine use could hasten the development of bacterial resistance, rendering it useless when required to treat infection.<sup>7</sup> One of the major risks of cotrimoxazole prophylaxis will be the potential for promoting cotrimoxazole resistance among common pathogens circulating in the community, as well as acquisition of infections caused by resistant organisms in the individual receiving prophylaxis. Several studies have shown an increase in resistance of pathogens to cotrimoxazole following widespread use of prophylaxis. However, the surprising observation has been that cotrimoxazole has had its effect preventing *Pneumocystis jirovecii* and other infections despite documented widespread cotrimoxazole resistance in certain settings. This was seen in the Zambian study<sup>2</sup> in HIV-infected children as well as in a Ugandan study.<sup>8</sup> Nevertheless, unless its benefit in terms of morbidity and survival for HIV-exposed (but negative) children can be shown to be considerable against the increase in resistance, it warrants a call for reassessment of the current guidelines. Furthermore, as Gill et al.<sup>1</sup> have pointed out, there is also the potential risk of widespread cotrimoxazole use fostering sulfadoxine-pyrimethamine

resistance in *Plasmodium falciparum* and impaired acquisition of natural immunity to malaria in infants.

### Benefits of breastfeeding

All of the studies that showed a positive impact of cotrimoxazole prophylaxis in HIV-infected children were mainly in children aged more than 12 months who were probably not being breastfed. Human breast milk has important protective benefits against enteric infections as well as chronic diseases later in life. Breastfed infants therefore have a reduced risk of infections such as diarrhoea and pneumonia due to the immune protection provided by breast milk and because they are not exposed to replacement milks that are often contaminated.<sup>9</sup> Recent programme experience from Botswana underlined the mortality risks of replacing breast milk with formula.<sup>10</sup> The risks were demonstrable despite provision of free formula and the availability of resources such as clean water beyond what may be affordable for many other developing countries. We therefore contend that HIV-exposed breastfed infants receive protection against numerous infectious pathogens and that this protection will over-shadow any possible benefits of cotrimoxazole prophylaxis without the added negative factors of: health system and drug costs; side-effects; and development of resistance to a potentially important, cheap antimicrobial drug.

### Conclusion

WHO's policy on cotrimoxazole prophylaxis was developed at a time when deter-

mination of HIV-risk status was based on maternal HIV-positive antibodies and risk of mother-to-child transmission of HIV was relatively high. Since that time much has changed. First, molecular diagnostic techniques make it possible to diagnose HIV early on in infancy and the logistics have been considerably simplified because the blood sample can be collected by a spot of blood from a heel prick which is stored on filter paper until tested by polymerase chain reaction. Second, there are far better options for prevention of mother-to-child transmission, i.e. ante- and intra-partum antiretroviral therapy as well as postpartum nevirapine prophylaxis for the infant during breastfeeding. Furthermore, several recent well designed prospective cohort studies have highlighted some of the detrimental effects of cotrimoxazole prophylaxis. Thus, on balance, WHO's policy has not evolved to accommodate this new information. While a year of cotrimoxazole prophylaxis may still be offered in situations where the likelihood of HIV transmission remains high, in other settings this recommendation no longer makes much sense.

Therefore we call for a thorough reappraisal of the current policy to limit the unnecessary use of cotrimoxazole prophylaxis in HIV-exposed infants. In addition, we add our voice to many calling for increased efforts in encouraging early diagnosis of HIV-infection in infants. This will allow timely introduction of antiretroviral treatment and cotrimoxazole prophylaxis for infected infants while limiting cotrimoxazole exposure in the uninfected group. ■

**Competing interests:** None declared.

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