Cotrimoxazole guidelines for infants who are HIV-exposed but uninfected: a call for a public health and ethics approach to the evidence

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WHO first recommended cotrimoxazole prophylaxis for all infants who are HIV-exposed but uninfected (HEU) in 2000, given the ability of this treatment to prevent mortality from pneumocystis pneumonia in adults living with HIV. Over the last 21 years, evidence has been generated from the use of cotrimoxazole prophylaxis in infants who are HEU, including two randomised controlled trials, which have shown no clinical benefit and an increase in antibiotic resistance and microbiome dysbiosis. Additionally, improvements in health care over the last two decades in terms of antiretroviral treatment and prophylaxis for mothers and infants, and notably improved vaccination programmes, have substantially reduced the risk of HIV transmission and the overall morbidity and mortality of infants who are HEU from pneumonia and diarrhoeal diseases. Here, we highlight these changes in health care alongside the unchanged cotrimoxazole prophylaxis guidelines and call for a change in these guidelines on the basis of a public health and ethics approach.

History and context of cotrimoxazole prophylaxis guideline reviews by WHO

In 2000, WHO first advised that all children and adults living with HIV should receive cotrimoxazole prophylaxis as part of a minimum package of care, after the publication of a study showing a decrease in mortality from pneumocystis pneumonia in adults living with HIV before access to triple antiretroviral therapy.[1] WHO also recommended that infants born to women living with HIV should receive cotrimoxazole prophylaxis until HIV infection had been reasonably ruled out and the risk of vertical transmission had ceased.[2] This was a reasonable recommendation, given the inadequate infant diagnostic testing and the absence of antiretroviral therapy for infants at that time.

In 2006, an updated WHO guideline[3] was released that used WHO grading terminology to explain that this guideline was a "strong recommendation" based on "very-low-quality evidence", followed by a guideline review in 2013.[4] Both of these reviews continued to recommend cotrimoxazole prophylaxis, despite the continued absence of evidence showing any benefit for children born to women living with HIV but who are uninfected, and despite the major changes in HIV care and treatment programmes that had occurred (notably interventions to diagnose and treat HIV infections in adults and children, interventions to prevent the vertical transmission of HIV, and major expansions in the availability of childhood vaccines, particularly the pneumococcal conjugate vaccine and the rotavirus vaccine). The 2013 guidelines advised that more evidence should be generated.

In response, two large randomised controlled trials (RCTs) were conducted to test whether or not there were benefits of cotrimoxazole prophylaxis for infants who are HIV-exposed but uninfected (HEU). Neither trial observed any benefits of cotrimoxazole prophylaxis in this population.[5,6] One RCT, done in Botswana,[5] was stopped early because of futility, finding no benefit of cotrimoxazole prophylaxis for cumulative mortality until 18 months of age, admission to hospital, diarrhoea, or pneumonia. The other RCT, done in South Africa,[6] showed the non-inferiority of not giving cotrimoxazole prophylaxis to infants who were HEU with regard to combined grade 3 and 4 pneumonia, diarrhoea, and all-cause mortality by 12 months of age. Additionally, two substudies within these trials identified harms (increased resistance to antibiotics and microbiome dysbiosis) arising from routine cotrimoxazole prophylaxis in children who are HEU.[7,8]

Despite the availability of new evidence from these two RCTs showing that routine cotrimoxazole prophylaxis is ineffective in children who are HEU, WHO guidelines have not changed and continue to recommend this intervention as of 2021.[9] The evidence from the two RCTs and the changes in health care require careful reconsideration of the probable effect of the existing approach—an exercise that has been undertaken by other advisory groups (eg, the South African Thoracic Society Guidelines no longer recommend routine cotrimoxazole prophylaxis for children who are HEU).[10]

Here, we outline advances in the context of health care relevant to cotrimoxazole prophylaxis as well as the current available data on the absence of a benefit and the potential harms of routine cotrimoxazole prophylaxis for infants who are HEU born to women living with HIV. We argue that WHO has missed a valuable opportunity for the timely, evidence-based revision of the cotrimoxazole prophylaxis guidelines for infants who are HEU, the negative effect of which is likely to cause increased health and economic burdens for families affected by HIV.

Advances in health care since 2000

Diagnosis of HIV infection in infants

An initial infant diagnosis used to be reliant on HIV antibody tests from 15 months of age, usually done using formal laboratory testing. Currently, many settings use point-of-care diagnostic testing for infants, often with

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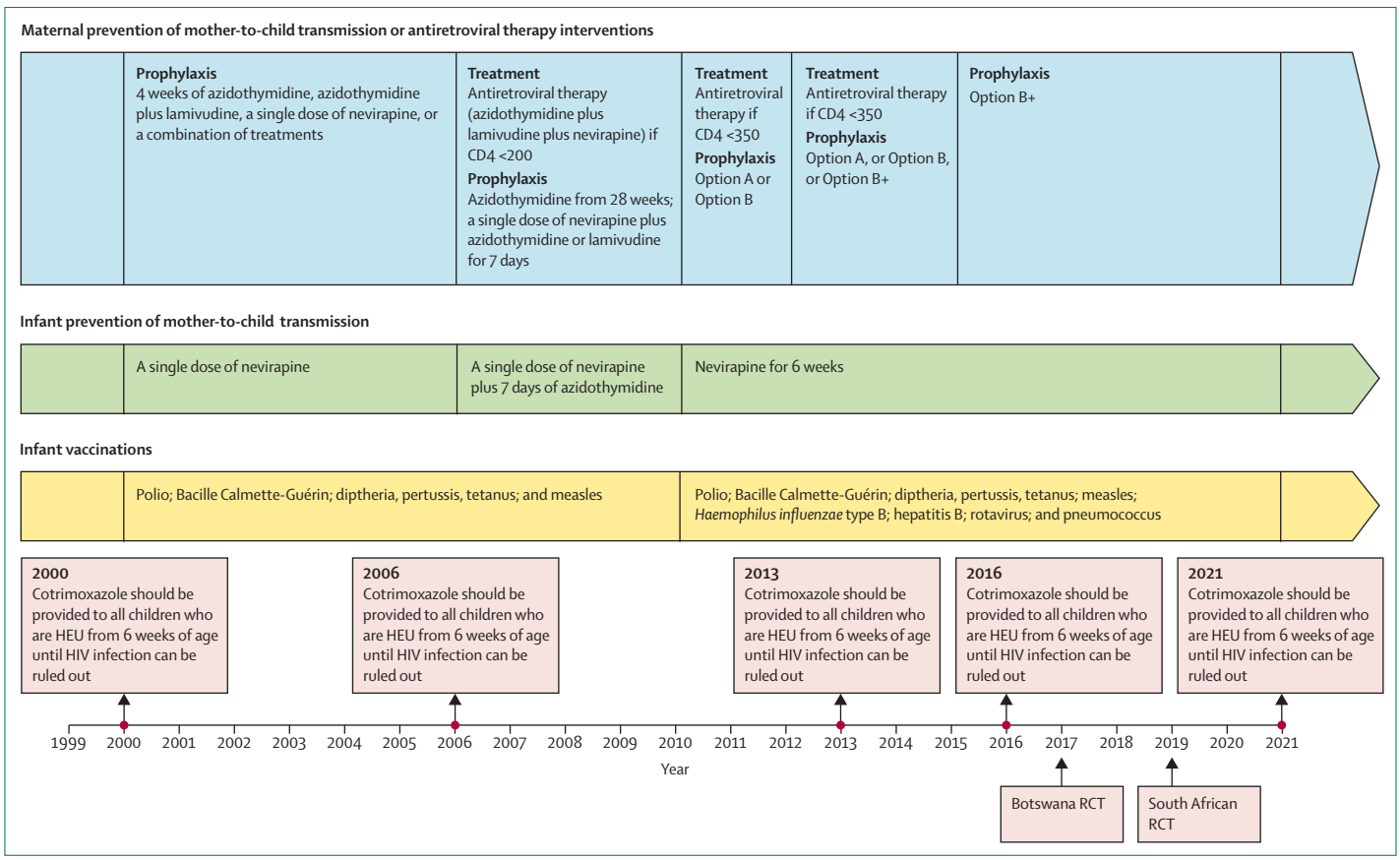

Figure: **Timeline of WHO cotrimoxazole guidelines versus changes in health care**
Timeline of WHO cotrimoxazole guidelines (in red boxes), compared with the timeline of WHO guideline changes for: maternal prophylaxis and antiretroviral therapy interventions (in blue), infant HIV prophylaxis (in green), and recommended infant vaccinations (in yellow). The timing of the two available RCTs from Botswana and South Africa that assessed the effect of cotrimoxazole prophylaxis on overall morbidity and mortality in children who are HEU is depicted beneath the x-axis. In the maternal intervention (blue) section: option A refers to azidothymidine from 14 weeks of gestation with a single dose of nevirapine plus 7 days of azidothymidine and lamivudine at birth. Option B refers to antiretroviral therapy from 14 weeks of gestation until the cessation of breastfeeding. Option B+ refers to antiretroviral therapy from 14 weeks of gestation plus lifelong antiretroviral therapy. HEU=HIV exposed but uninfected. RCT=randomised controlled trial.

infant HIV testing first done at the time of delivery, or within the first 10 weeks of life.[11]

Improved prevention of mother-to-child transmission

In 2000, the vertical transmission of HIV was estimated to occur in more than 30% of all births from mothers living with HIV, which has now decreased substantially since the introduction of antiretroviral therapy for mothers and the optimisation of antiretroviral prophylactic regimens for their infants. The estimated mother-to-child-transmission rate in 21 focus countries (which are home to 84% of the global number of pregnant women living with HIV, and 81% of children living with HIV) is on average 10% of all births from women living with HIV (8–13%).[12] A study in Zimbabwe done just after the roll-out of Option B+ (maternal antiretroviral therapy from 14 weeks of gestation plus lifelong antiretroviral therapy) showed an intrauterine transmission rate of 0·88%, an intrapartum transmission rate of 0·22%, and a post-partum transmission rate of 0·44%.[13]

By 2010, WHO recommended Option A (maternal azidothymidine from 14 weeks of gestation, with a single infant dose of nevirapine plus 7 days of azidothymidine and lamivudine at birth) or Option B (maternal antiretroviral therapy from 14 weeks of gestation until the cessation of breastfeeding) for pregnant women living with HIV. Antiretroviral prophylaxis was provided during breastfeeding either to the infant (Option A) or the mother (Option B).[14] By 2013, Option B+ was recommended, whereby mothers were offered lifelong treatment. A new addition is that lifelong antiretroviral therapy is provided as early as possible, ideally initiated before or during pregnancy to optimise maternal health and prevent vertical transmission.[15]

Improvements in antiretroviral therapy have also reduced pneumonia mortality in sub-Saharan Africa. Before the introduction of antiretroviral therapy up until 2010, non-pneumocystis pneumonia mortality prevalence in adults and children living with HIV was 16·3% (95% CI 6·3–29·4%), compared with an overall prevalence of 6·5% (95% CI 1·8–13·4%) in the post-antiretroviral

therapy era of after 2010.[16] In South Africa, the improved prevention of mother-to-child transmission and vaccination programmes have led to a 50% decrease in pneumonia incidence in children younger than 5 years, with an estimated 71% reduction in the number of children living with HIV by 2015.[17] Additionally, the causes of pneumonia were similar between children who are HEU and children who are unexposed to HIV.[18] A Zimbabwean study on Option B+ reported a 6-month mortality rate for infants born to women living with HIV of 0·88% in 2018, contrasting notably with the pre-antiretroviral therapy mortality rate of 11·8% reported in 2004.[13] Changes in prevention of mother-to-child transmission programmes for both infants and mothers, in addition to childhood vaccination improvements, are illustrated in the timeline in the figure.

Availability of an expanded repertoire of childhood vaccines

In 2000, the routine childhood vaccines used on the African continent were polio; Bacille Calmette-Guérin; measles; and diphtheria, pertussis, and tetanus. Since then, four vaccines have been added: hepatitis B, rotavirus, pneumococcus, and *Haemophilus influenzae* type b. Several studies attest to the benefits of these, with reduced pneumonia and diarrhoeal morbidity and mortality outcomes. A Botswanan study in infants who are HEU showed substantial reductions in admissions to hospital and deaths from diarrhoea and pneumonia in the new vaccine era compared with before the introduction of the new vaccines.[19] The Global Burden of Disease data have also shown decreases in pneumonia and diarrhoeal morbidity and mortality outcomes in low-income and middle-income countries.[20] Between 2005 and 2015, global pneumococcal deaths declined by 51% (7–74%) in HIV-uninfected children and 75% in HIV-infected children, whereas *Haemophilus influenzae* type b deaths in children declined by an estimated 90% (78–96%).[21] In South Africa, the introduction of the pneumococcal vaccination has reduced admissions to hospital for all-cause pneumonia by 33% for children living with HIV and 39% in children not living with HIV.[10]

Increased support for breastfeeding

Considerable evidence has emerged on the short-term and long-term benefits of breastfeeding for improving the health of infants.[22,23] Evidence on the rates of HIV transmission via exclusive breastfeeding, and later with the availability of antiretroviral therapy for mothers and antiretroviral prophylaxis for infants, has resulted in substantial changes in WHO breastfeeding and HIV guidelines over the last two decades. Previously, breastfeeding was largely discouraged among women living with HIV;[24] however, since 2016, women living with HIV have been encouraged to exclusively breastfeed for 6 months and continue breastfeeding up to 24 months at the same time as maintaining viral suppression, as the best option for infant HIV-free survival.[25] Supporting evidence for this guidance was provided by the results of a large individual pooled analysis of African and Asian studies that reported that the survival of children who are HEU could be substantially improved if women living with HIV were virally suppressed and were supported to breastfeed.[26]

Evidence of benefits of cotrimoxazole prophylaxis in other infants who are vulnerable or immune-compromised

It is valuable to examine whether there is information on the benefits of cotrimoxazole prophylaxis in infants who are vulnerable or immune-compromised other than those who are HEU. A commentary encouraging the expansion of cotrimoxazole prophylaxis in low-income and middle-income countries[27] hypothesised that other vulnerable infants might also benefit from cotrimoxazole prophylaxis. However, two studies have investigated the possible benefits of cotrimoxazole prophylaxis, one in infants with severe acute malnutrition[28] and the second in children admitted to hospital with severe anaemia.[29] Neither study found any benefit of cotrimoxazole prophylaxis.

Harms of cotrimoxazole prophylaxis in children

The routine administration of cotrimoxazole prophylaxis has been shown to pose substantial hazards to the healthy development of children born to women living with HIV, given associations between cotrimoxazole prophylaxis and antibiotic resistance and potentially deleterious effects on infants' developing microbiome.

Antibiotic resistance

A notable harm associated with routine cotrimoxazole prophylaxis is an increase in antibiotic drug resistance.[7,8] In an RCT in Botswana, cotrimoxazole prophylaxis was associated with amoxicillin resistance.[8] This finding is concerning, because amoxicillin is a first-line treatment for infant pneumonia in many primary health-care guidelines. In the WHO AWaRe antibiotic recommendations, amoxicillin has been assigned to an access category, meaning that countries are required to ensure its availability and uninterrupted supply chains because of its safety, efficacy, and "lower potential for resistance".[30,31] Cotrimoxazole prophylaxis studies have also reported increased resistance to other antibiotics (including chloramphenicol, ciprofloxacin, nalidixic acid, and ampicillin).[32]

It has been suggested that antibiotic resistance might not persist after cotrimoxazole cessation; however, the time period of persistence after antibiotic cessation is confounded by persister cells in heterogeneous bacterial populations.[33] Furthermore, cotrimoxazole prophylaxis is administered during a crucial developmental time in an infant's life, when they are at a high risk of severe infections. This is not an appropriate time to cycle

through second-line and potentially more toxic antibiotics. The widespread use of antibiotic prophylaxis also increases the prevalence of antimicrobial resistance in the wider population and hence the risk of acquiring a resistant organism, a concern raised in the MORDOR trial on the mass administration of azithromycin to children.[34] This finding is concerning for countries with high numbers of children who are HEU (including Eswatini, Botswana, South Africa, Lesotho, Namibia, and Zimbabwe). There is an urgent need for careful antibiotic stewardship and concentrating on targeted interventions where there is irrefutable evidence that the benefits override the harms.

Microbiome development

Cotrimoxazole prophylaxis interferes with healthy infant microbiota development and has been associated with disruptions to age-appropriate changes and increases in dysbiosis over time.[7] Antibiotics can cause changes to the microbiota in infancy,[35] with the first 6 months of life being the most dynamic period of microbiome development. Dysbiosis can be magnified if antibiotics are frequently administered, if there are underlying gastrointestinal disturbances, or in the presence of an inadequate diet.[35]

There are substantial data linking dysbiosis to disease and neurological outcomes, many associations of which are still under investigation. The TEDDY study, done in infants who were unexposed to HIV, reported decreases in *Bifidobacterium* species in the microbiome, suggesting that they are susceptible to being outcompeted by other species after antibiotic treatment. Given their dominance in typical developing gut microbiota and the finely tuned balance of metabolic interactions with breastmilk, this finding underscores the need to approach antibiotic treatment and prophylaxis in early childhood with care, especially during breastfeeding.[36]

Given the negative effect of even short courses of antibiotics on the microbiome, it seems unwise to assume that months of daily antibiotics during a crucial developmental period will not have a negative effect on the microbiome, an effect that might only be noticeable years later when other inter-related factors might preclude the assignment of causality to antibiotics.

Considerations for regions with poor prevention of mother-to-child transmission coverage

A key component in the argument in support of routine cotrimoxazole prophylaxis for all infants born to women living with HIV is that in settings with inadequate prevention of mother-to-child transmission and an absence of early infant diagnosis programmes, undiagnosed infants living with HIV could benefit from cotrimoxazole prophylaxis. However, in settings where HIV testing services and their links to treatment initiation are poor, it should not be assumed that these same untested children will be prescribed cotrimoxazole, since they are unlikely to be accessing any form of care. Most infants will be uninfected with HIV but are being exposed to a potentially harmful medication with no individual benefit. Moreover, the subset of infants who even potentially stand to benefit are those who acquire an infection but were missed by diagnostic services. If the key concern is children living with undiagnosed HIV, then the most appropriate solution is identifying both infants at a high risk of infection and mothers at a high risk of infection who are negative for HIV and offering them more frequent HIV testing.

It is well established that paediatric antiretroviral therapy substantially improves outcomes in children, especially when the treatment starts early in life. Additionally, cotrimoxazole prophylaxis is not optimal treatment for an HIV infection; rather, timely HIV identification and antiretroviral therapy initiation is key. The primary focus regarding infants who acquire HIV is to prioritise their diagnoses, initiate early treatment, support the mother with breastfeeding, and ensure timely vaccinations. Cotrimoxazole prophylaxis given in the context of these interventions might add additional benefits and we are not suggesting that it should be withheld from infants on antiretroviral therapy. However, cotrimoxazole prophylaxis is an inappropriate substitute for these more established protective strategies, and continual reliance on cotrimoxazole prophylaxis as an alternative strategy reinforces a misconception that it is a sufficient intervention for these highly vulnerable infants. As far back as 2004, Gill and colleagues[37] suggested that the most logical option would be to directly reduce the risk of infant HIV infection in HIV-exposed infants by using nevirapine (and therefore indirectly reducing their pneumonia risk), rather than to use cotrimoxazole to protect against pneumonia in only a few infants. Furthermore, mother–child pairs that are not adherent to the prevention of mother-to-child transmission are unlikely to be any more adherent to cotrimoxazole prophylaxis. Persevering with a suboptimal intervention detracts staff attention from efforts to strengthen the prevention of mother-to-child transmission, early infant diagnosis, maternal viral load monitoring, and to prompt antiretroviral therapy initiation.

The better option is to increase efforts to diagnose infants who are living with HIV and enrol them in care and treatment services. Emphasis on these efforts would remove the ethical dilemma of providing non-beneficial and potentially harmful cotrimoxazole to infants who are HEU with the intention of protecting those who might become infected with HIV. Based on the prevention of mother-to-child transmission rate from 21 focus countries, assuming a scenario of 1000 infants who are exposed to HIV, conservatively, some 100 infants (10%) might be infected by 6 months. This calculation equates to 900 infants who are HEU being administered cotrimoxazole prophylaxis with no benefit to themselves

and possible harm being caused. Standard public health policy dictates that policies that are in the interest of most of a population are to be implemented, especially if there is more effective clinical management available for the affected minority.

Conclusion

Given the evidence that cotrimoxazole resistance could lead to the diminished effectiveness of cotrimoxazole and other antibiotics used for treating infections caused by drug-resistant bacteria, and the disruption of the microbiome induced by cotrimoxazole, the current policy of continuing cotrimoxazole prophylaxis in infants who are HEU can potentially result in substantial adverse effects. It is also necessary to harmonise policies across different WHO departments. The prevention of mother-to-child transmission policy promotes exclusive breastfeeding for 6 months and continued breastfeeding for 24 months, and mothers are informed that their risk of infecting their infant is low. However, the cotrimoxazole prophylaxis policy implies that the risk of HIV infection is high. WHO also has a strong antimicrobial stewardship programme, but in this case, the growing body of evidence of potential drug resistance as an unintended consequence of cotrimoxazole prophylaxis has been discounted.

Several notable advancements have been made with regard to mother-to-child transmission over the last two decades. These advancements include a 70% reduction in new paediatric infections globally between 2000 and 2015, with vertical transmission declining from more than 30% to less than 10%. A universal test and treat method is implemented in most countries, with antiretroviral therapy regimens substantially improved (with both lower pill counts and higher barriers to resistance). Early infant diagnosis (at birth or within the first 10 weeks) is implemented in many countries. When the cotrimoxazole prophylaxis policy was introduced by WHO, more than 500 000 children were becoming infected with HIV annually. By 2019, however, despite the absolute number of women infected with HIV being consistently more than 1 million per year, only 160 000 infants were born with HIV. Given the substantially higher percentage of infants who are HEU compared with those who become HIV infected, and the evidence provided from two RCTs on the absence of benefit for infants who are HEU as well as the probable harm of this intervention, there is an urgent need for the current cotrimoxazole prophylaxis policy to be reversed for infants who are HEU. Although research has shown that infants who are HEU are at a higher risk of morbidity and mortality, aspects of maternal health (eg, low CD4 count and high viral load) are key drivers of this excess risk.[26,38] Cotrimoxazole prophylaxis does nothing to improve maternal health and detracts from implementing programmes that are beneficial to both maternal and child health. The money and time saved from procuring, transporting, storing, and administering cotrimoxazole prophylaxis could be used for activities with a known benefit, including strengthening the prevention of mother-to-child transmission and early infant diagnosis services, maternal viral load monitoring, strengthening paediatric care and treatment programmes, and promoting and supporting breastfeeding. Until this policy is re-examined, at the very least, there needs to be transparent information provided to the infants' caregivers about the absence of proven benefit and potential harms of cotrimoxazole prophylaxis, with receipt of written informed consent before the intervention is provided.

Contributors

AC and BD conceptualised the manuscript. BD, LK, ES, HM, AG, UF, SYE, and AC contributed to the literature review, writing, reviewing, and editing of the document.

Declaration of interests

We declare no competing interests.

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