POLICY BRIEF: CHANGING THE COTRIMOXAZOLE PROPHYLAXIS GUIDELINES FOR HIV EXPOSED-UNINFECTED INFANTS - SOUTH AFRICAN EVIDENCE

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BACKGROUND

The World Health Organization (WHO) guidelines recommend that all HIV-exposed infants, including HIV-exposed uninfected infants (HEUs), born to HIV positive mothers receive co-trimoxazole (CTX) prophylaxis, commencing at 4–6 weeks of age and continued until HIV infection can be excluded. This guideline was based on efficacy data from a single trial studying antiretroviral-naïve, HIV positive children who were protected from Pneumocystis pneumonia (PCP) by CTX (Chintu *et al.*, 2004). Guidelines for CTX prophylaxis were established at a time when there was limited access to HIV diagnostic testing to identify infants living with HIV (testing could only occur after 24 months of age), and prevention of mother-to-child transmission of HIV (PMTCT) drug interventions were less effective than current regimens.

Previous studies have shown inconsistent effectiveness of CTX prophylaxis against malaria and bacterial infections in some populations (Coutsoudis *et al.*, 2011; Coutsoudis *et al.*, 2005; Sandison *et al.*, 2011; Taha *et al.*, 2011; Thera *et al.*, 2005). Although CTX appears to convey benefit in relation to reduction in malarial morbidity, there is inadequate evidence supporting the benefit of CTX prophylaxis in breastfed HEU infants, in terms of overall morbidity and mortality.

THIS POLICY BRIEF IS DRAWN FROM:

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D'Souza,A., E. Moodley-Govender, *et al.* (2019) "Cotrimoxazole prophylaxis increases resistance gene prevalence and α-diversity but decreases β-diversity in the gut microbiome of HIV-exposed, uninfected infants. *Clinical Infectious Diseases,* DOI: https://doi.org/10.1093/cid/ciz1186.

Currently, South Africa's well-established PMTCT program has resulted in low vertical HIV transmission rates, with routine early infant diagnostic testing resulting in timeous lifelong antiretroviral treatment (ART) and CTX prophylaxis for HIV infected infants (Barron *et al.*, 2013; Goga *et al.*, 2018; Sherman *et al.*, 2014). Since there is greatly improved surveillance and so few infants being newly infected with HIV, South Africa needed to consider the appropriateness and cost-effectiveness of a public health "blanket' approach of providing CTX prophylaxis to all HIV-exposed infants, particularly with recent concerns regarding antimicrobial resistance (Coutsoudis *et al.*, 2010; Gill *et al.*, 2004; Weerasuriya *et al.*, 2010).

HYPOTHESIS AND OBJECTIVES

The study was designed as a randomized controlled non-inferiority trial to test the following hypothesis: The breastfed HEU infant who does not receive CTX will not have an inferior outcome in terms of the incidence of grade 3 or 4 common childhood illnesses or mortality compared to the infant who does receive CTX. The non-inferiority trial design was chosen as the absence of CTX was viewed as the alternative intervention to be compared to standard-of-care. The primary objective was to compare the incidence of grade 3 and grade 4 common childhood illnesses or all-cause mortality until 12 months of age in HEU infants receiving CTX or no CTX. Consequently, the primary endpoint was incidence of grade 3 and grade 4 common childhood illnesses or all-cause mortality until 12 months of age. For the proposed study, common childhood illnesses were defined as pneumonia and diarrhea (Coutsoudis *et al.*, 2016). A small sub-study investigated the effect of CTX prophylaxis on the infant microbiome.

METHODS

- Study conducted over a five-year period, between October 2013 and October 2018 at the Lancers Road and Cato Manor clinics in Durban, South Africa.
- Enrolled healthy, breastfeeding infants born to HIV positive mothers (actively in PMTCT follow-up); infants were HIV negative prior to the 6 week enrollment visit and were followed up until 12 months of age (Figure 1).
- A sample size of approximately 1298 (649 infants per study arm) was chosen to select a non-inferiority bound of 5% and assumed power of 0.90, with 10% anticipated loss to follow-up, and an α level of 0.025. A non-inferiority bound of 5% was selected to rule out a clinically meaningful benefit of co-trimoxazole.
- Primary analysis was intent-to-treat and analysed all available data as randomized.
- Primary endpoints were analyzed using the Kaplan-Meier time to event approach.
- The risk difference for the primary non-inferiority analysis was calculated as the cumulative probability of the endpoint from the failure function of the Kaplan-Meier curve in the No CTX arm minus the cumulative probability in the CTX arm.
- Time to primary and secondary endpoints were compared between treatment arms using Cox proportional hazard models.

SCREENING VISIT (BIRTH – 6 WEEKS)
Informed Consent
Infant HIV test (if no birth PCR)
Screening questionnaire

ENROLLMENT (6 WEEKS)
Randomized to study arm

Arm 1: CTX until all exposure to HIV has ceased and the infant is confirmed to be HIV uninfected (through 6 weeks after last exposure to breast milk): 20mg trimethoprim/100mg sulfamethoxazole orally if less than 6 months of age or less than 5kg; and 40mg trimethoprim and 200mg sulfamethoxazole orally if older than 6 months of age or greater than 5kg; once daily.

Arm 2: No CTX.

STUDY VISIT PROCEDURES (6, 10 AND 14 WEEKS AND MONTHLY UNTIL 12 MONTHS)
Vaccinations (if indicated)

Evaluated for:
Interval illness
Signs and symptoms of CTX toxicity
CTX adherence
Concomitant medication use
HIV infection status (if indicated)
Anthropometry
Breastfeeding status

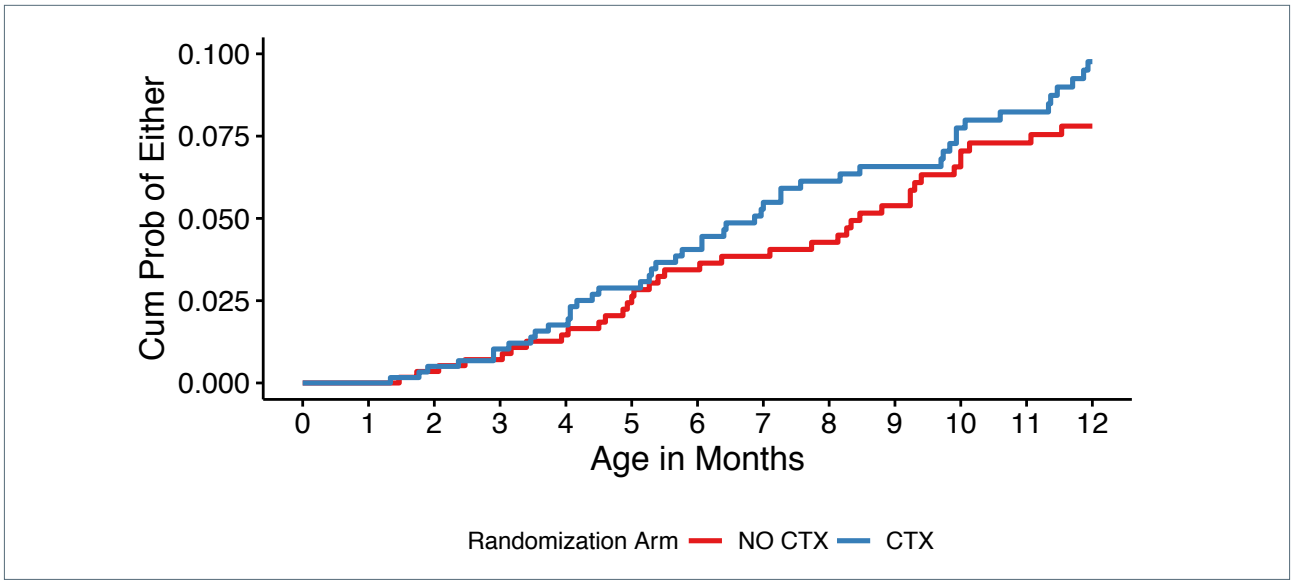
Figure 1: Study Procedures

The sub-study compared whole metagenome sequencing and analysis of stool samples from 63 HEU infants at baseline (6 weeks), 4 months and 6 months. The sub-study compared gut microbial taxonomic composition, microbiome functional genes, and antibiotic resistomes.

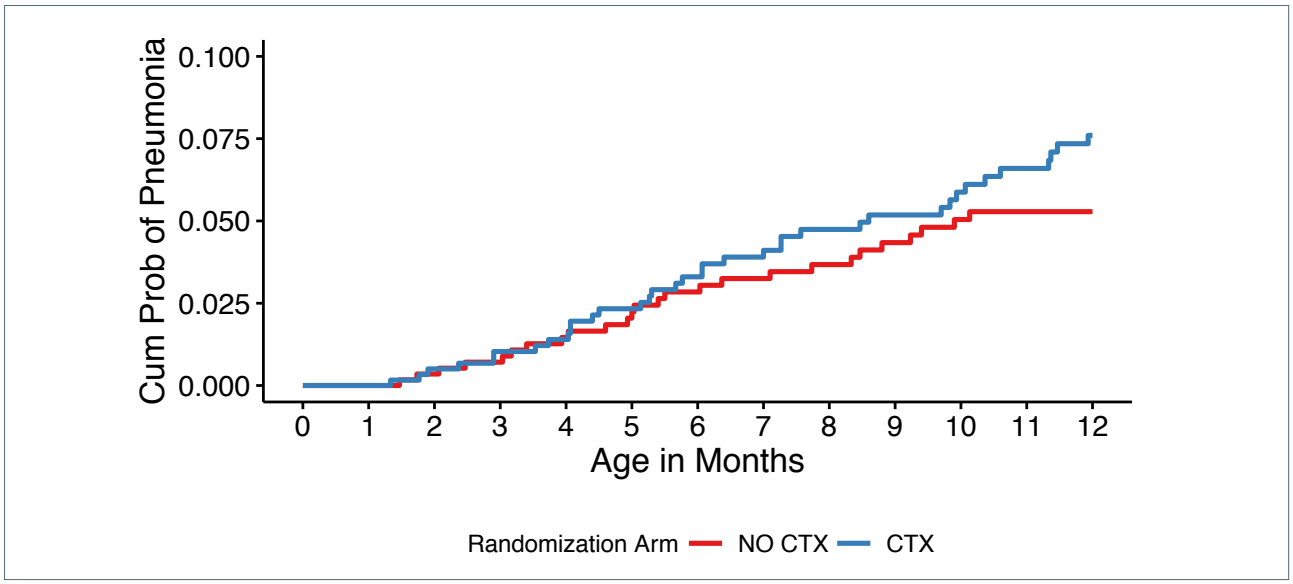
SUMMARY OF FINDINGS

- A cohort of 1219 HIV-exposed infants were enrolled between October 2013 and April 2018 (611 in the CTX arm and 608 in the No CTX arm; 653 male infants vs 566 female infants; mothers median CD4 count was 436 (IQR: 302-574) in the CTX arm vs 475 (IQR: 340-616) in the No CTX arm (p: 0.009).
- The unadjusted hazard ratio of the primary endpoint (incidence of grade 3 and grade 4 common childhood illnesses or all-cause mortality until 12 months of age) was 1.23 (95% CI: 0.81-1·87) in the CTX arm and 1.25 (95% CI: 0.80 – 1.97), after adjusting for mothers' CD4 count.
- There were no significant differences across the arms in the cumulative probabilities of these endpoints over time to 12 months (Figure 2).
- Figure 3 presents a visual schematic demonstrating that no CTX is NOT INFERIOR to CTX prophylaxis (Figure 3)

(A)



(B)



(C)

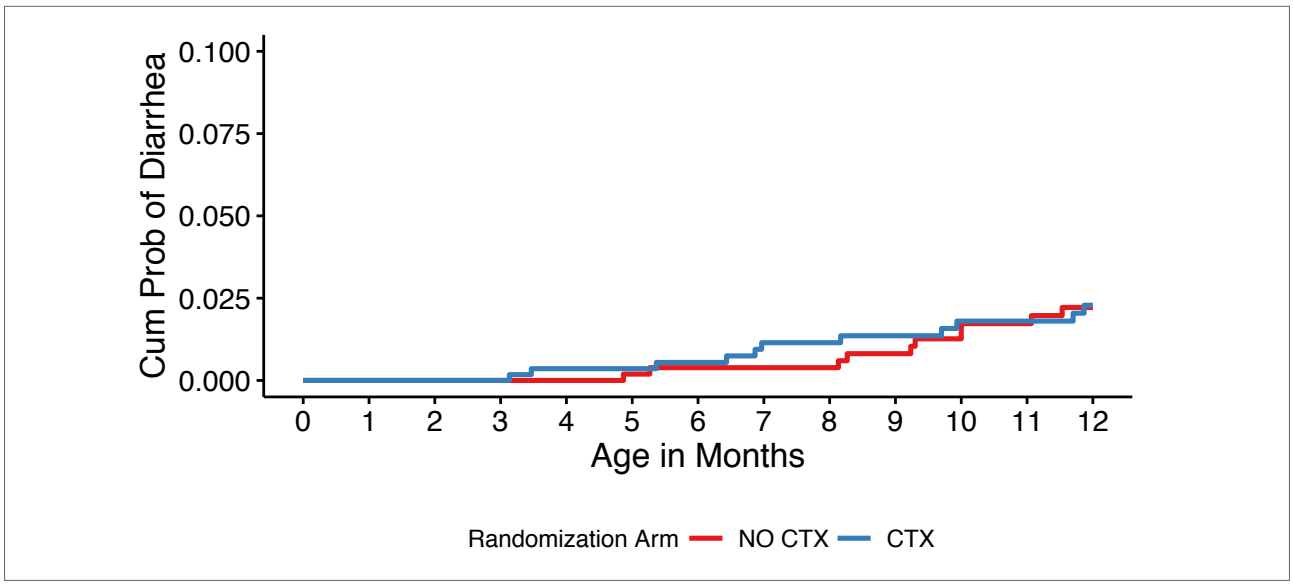


Figure 2: *Kaplan-Meier curves of the cumulative probability of the combined outcome (i.e. grade 3 or 4 pneumonia or diarrhea or death) (A), grade 3 or 4 pneumonia (B) and grade 3 or 4 diarrhea (C). In all panels, the blue line represents children in the CTX arm and the red line represents children in the no CTX arm.*

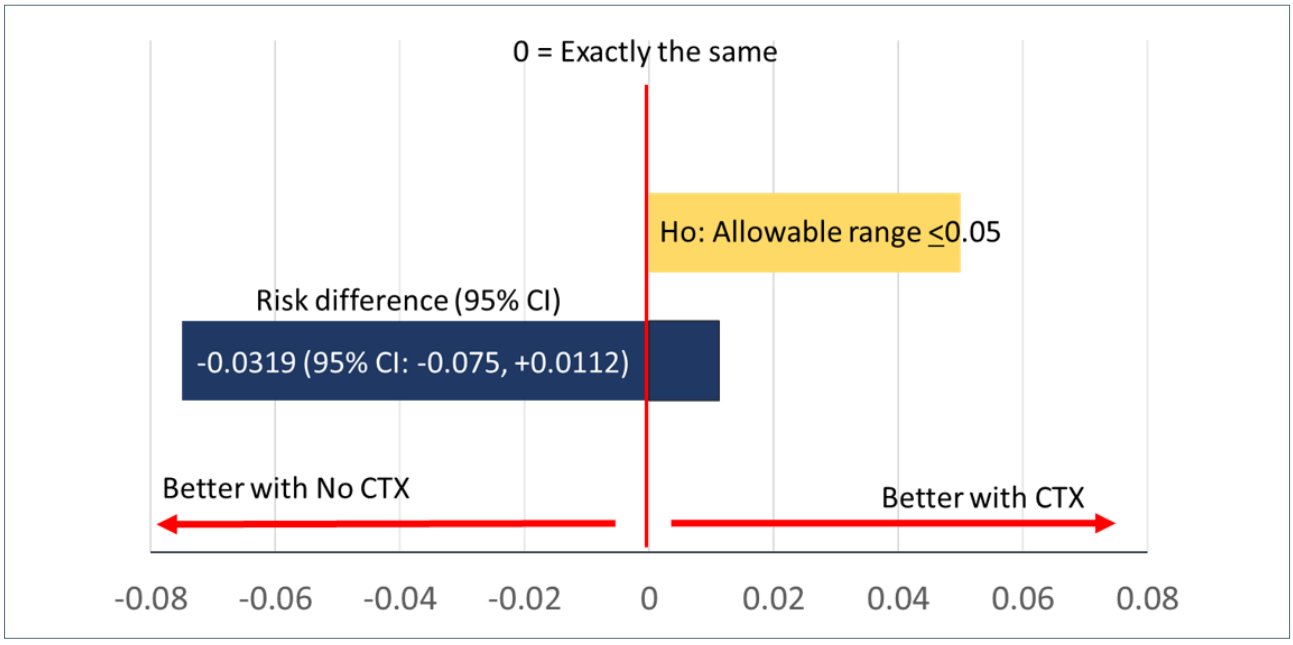


Figure 3: Figure 3: Schematic explaining the interpretation of the results in terms of the non-inferiority design.

- The protocol specified that a <0.05 increase in the rate of events (on an additive scale) in the CTX arm compared to the no CTX arm was acceptable to conclude that not giving CTX was not inferior to (equal to) giving CTX to HEU infants (yellow bar).
- From the results of the trial, the risk difference was calculated i.e. rate of events in the No CTX arm minus the rate of events in the CTX arm.
- The rate in the No CTX arm was 0.0795 and in the CTX arm 0.114 yielding a risk difference of -0.0319 (i.e. lower in the No CTX arm) (blue bar).
- This illustrates that the rate of events in the no CTX arm lies within and below the allowed 0.05 increase in the rate of events compared to the CTX arm.

Sub-study findings: The sub-study analysis showed that infants taking CTX had significantly higher resistance gene abundance than infants not taking CTX. Additionally, infants taking CTX had decreased inter-individual gut microbiome taxonomic, functional taxonomic, and resistance gene diversity, which is consistent with persistent antibiotic selection pressure. Over time, the microbiome characteristics of infants taking CTX became increasingly similar to one another and less diverse compared to infants that did not receive CTX. These alterations of the microbiome are considered to be unfavourable and may have consequent negative health impacts.

LIMITATIONS

- Not placebo controlled, as even the use of a placebo (usually a sugar solution) had the potential to interfere with the gut and disrupt the benefits of exclusive breastfeeding, and may have introduced bias as we were interested in evaluating the absence of CTX.
- Cotrimoxazole adherence was self-reported by mothers or caregivers. Reported rates of adherence were high with <10% of those prescribed CTX reporting substantial non-adherence (more than a week of missed doses). However, this is still likely to represent what would happen in reality in a PMTCT program.

- This study did not include low birth weight infants or multiple births, as it was not powered to investigate the effect of CTX in this small group.
- The study excluded all infants who were HIV infected at baseline.

STRENGTHS

- Study was conducted at the epicenter of the HIV epidemic (Durban, South Africa), therefore results are likely to be generalizable to the rest of South Africa.
- Confirms results recently published from a CTX study in Botswana (Lockman *et al.*, 2017), which showed no difference in hospital admissions (12.5% in CTX arm vs 17.4% in the placebo arm; p=0.19) or in grade 3 or 4 clinical adverse events (16.5% vs 18.4%; p=0.18).
- The study used very stringent criteria for deciding on clinical benefit of CTX; the 5% non-inferiority bound is equivalent to allowing a relative risk (RR) of 1.71 associated with the absence of CTX. The choice of delta as large as five percentage points (RR=1.71) was based on the need to provide clear benefits for a country administering CTX prophylaxis.

CONCLUSIONS

- This study has shown that **there is no benefit of daily cotrimoxazole among HIV-exposed uninfected breastfed infants**, whose mothers are accessing a PMTCT program, and adhering to lifelong ART in a non-malaria area.
- Consequently, cotrimoxazole prophylaxis should be removed from the PMTCT program in non-malaria countries.
- The benefits of removing the CTX prophylaxis are:
  - cost-savings;
  - reduction in adverse events; and
  - a likely increase in quality of life of infants.
- Non-malaria, countries should rather focus their limited resources (both human and financial) on strengthening breastfeeding programs, ART adherence and viral load monitoring in mothers.
- The implications of the findings of increased resistance to CTX are serious since some evidence exists that cotrimoxazole resistance also confers resistance against other important antibiotics used during childhood, for common illnesses viz. ampicillin, chloramphenicol and ciprofloxacin.
- Since antibiotic resistance is a growing threat, and **since these studies have shown CTX prophylaxis increases antibiotic resistance genes while showing no clinical benefit for HEU infants in non-malaria countries, these data reiterate the call for revising the current cotrimoxazole guidelines for HEU infants when mothers are actively receiving ART**.

POLICY IMPLICATIONS

1. CTX should not be started in HEUs that have a negative HIV test at birth, and whose mothers are receiving and adherent to lifelong ART.
2. Breastfeeding mothers should have a viral load test performed at all antenatal visits, to ensure suppressed viral load.
3. CTX prophylaxis should not be provided for HEU infants without accompanying risk factors that place them at increased risk of HIV acquisition (such as malaria-endemic areas / untreated mothers / mother not on adequate treatment / mother not virally suppressed).

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