The expanding role of co-trimoxazole in developing countries

James A Church, Felicity Fitzgerald, A Sarah Walker, Diana M Gibb, Andrew J Prendergast

Co-trimoxazole is an inexpensive, broad-spectrum antimicrobial drug that is widely used in developing countries. Before antiretroviral therapy (ART) scale-up, co-trimoxazole prophylaxis reduced morbidity and mortality in adults and children with HIV by preventing bacterial infections, diarrhoea, malaria, and *Pneumocystis jirovecii* pneumonia, despite high levels of microbial resistance. Co-trimoxazole prophylaxis reduces early mortality by 58% (95% CI 39–71) in adults starting ART. Co-trimoxazole provides ongoing protection against malaria and non-malaria infections after immune reconstitution in ART-treated individuals in sub-Saharan Africa, leading to a change in WHO guidelines, which now recommend long-term co-trimoxazole prophylaxis for adults and children in settings with a high prevalence of malaria or severe bacterial infections. Co-trimoxazole prophylaxis is recommended for HIV-exposed infants from age 4–6 weeks; however, the risks and benefits of co-trimoxazole during infancy are unclear. Co-trimoxazole prophylaxis reduces anaemia and improves growth in children with HIV, possibly by reducing inflammation, either through direct immunomodulatory activity or through effects on the intestinal microbiota leading to reduced microbial translocation. Ongoing trials are now assessing the ability of adjunctive co-trimoxazole to reduce mortality in children after severe anaemia or severe acute malnutrition. In this Review, we discuss the mechanisms of action, benefits and risks, and clinical trials of co-trimoxazole in developing countries.

Lancet Infect Dis 2015; 15: 327–39

Published Online November 14, 2014 http://dx.doi.org/10.1016/S1473-3099(14)71011-4

This online publication has been corrected. The corrected version first appeared at thelancet.com/infection on January 22, 2015

Centre for Paediatrics, Blizard Institute, Queen Mary University of London, London, UK (J A Church MB, A J Prendergast DPhil); **UCL Institute of Child Health, London, UK** (F Fitzgerald MRCPCH); **MRC Clinical Trials Unit at University College London, London, UK** (A S Walker PhD, D M Gibb MD, A J Prendergast); **and Zvitambo Institute for Maternal and Child Health Research, Harare, Zimbabwe** (A J Prendergast)

Correspondence to: Dr Andrew J Prendergast, Centre for Paediatrics, Blizard Institute, Newark Street, London E1 2AT, UK **a.prendergast@qmul.ac.uk**

Introduction

Since the 1960s, a fixed-dose combination of trimethoprim-sulfamethoxazole (co-trimoxazole) has been used as a broad-spectrum antibiotic in many settings.[1] After its initial use as empirical therapy for urinary and lower respiratory tract infections, it was shown to also have useful prophylactic activity against *Pneumocystis carinii* (now *jirovecii*) pneumonia in patients receiving chemotherapy.[2,3] Use of co-trimoxazole increased greatly from the 1980s during the HIV epidemic, because it provided protection against various opportunistic infections, and reduced mortality and morbidity in the pre-antiretroviral therapy (ART) era.[4–8] However, even with the advent of effective ART regimens, co-trimoxazole continues to provide important benefits for individuals with HIV, particularly in developing countries. Co-trimoxazole is a unique compound that combines broad antimicrobial activity with immunomodulatory properties. Furthermore, it is well tolerated, widely available, off-patent, and inexpensive, which makes it ideal for use in low-income settings. This Review focuses on historical evidence and clinical trials that emphasise the expanding role of co-trimoxazole in developing countries.

Antimicrobial properties of co-trimoxazole

Trimethoprim and sulfamethoxazole synergistically block microbial synthesis of folic acid, a vital cofactor in the manufacture of thymidine and purines. Sulfamethoxazole is a competitive inhibitor of dihydrofolic acid synthesis, and trimethoprim acts downstream of sulfamethoxazole to inhibit production of the physiologically active tetrahydrofolic acid. Although each agent alone is bacteriostatic, their blockade of two sequential enzymes results in bactericidal activity when combined.[1,9] Furthermore, the combination of two antimicrobials was postulated to decrease the emergence of resistance, although in certain circumstances (such as the treatment of urinary tract infections), trimethoprim is the more active component.[1,10] Although there is now high antimicrobial resistance in many settings, co-trimoxazole has intrinsic activity against a broad spectrum of bacterial, fungal, and protozoal pathogens[9,11] (panel 1).

Co-trimoxazole in HIV infection

Co-trimoxazole in the pre-ART era

In developed countries, co-trimoxazole prophylaxis reduced mortality in adults and children with HIV in the pre-ART era, predominantly by preventing *Pneumocystitis jirovecii* pneumonia.[4,14,15] Before the widespread scale-up of ART, co-trimoxazole was similarly shown to reduce morbidity and mortality in adults and children with HIV in sub-Saharan Africa.[6,16–18] The benefits of co-trimoxazole in this setting were due to substantial reductions in several infections, not only *P jirovecii* pneumonia.[16–19] Children with HIV Antibiotic Prophylaxis (CHAP) was a double-blind, randomised, controlled trial enrolling Zambian children aged more than 12 months to either co-trimoxazole or placebo, before the availability of ART.[6] The hazard ratio (HR) for death after a median of 19 months was 0·57 (95% CI 0·43–0·77; p=0·0002) for co-trimoxazole versus placebo, and hospital admission rates were reduced by 23%, irrespective of age or baseline CD4 cell count (69% of children had CD4 cell count <15% of the total lymphocyte count). Most of the excess deaths in the placebo group were from pneumonia (mostly diagnosed presumptively), and antibiotic prescription rates were significantly higher, which suggests that co-trimoxazole has protective benefits against bacterial infections in sub-Saharan Africa.[20]

Prophylaxis against *P jirovecii* pneumonia is important in developing countries, although initial reports showed that this infection was uncommon in sub-Saharan African adults.[21–25] The risk of *P jirovecii* pneumonia is related to age, and infants with HIV are especially vulnerable, irrespective of CD4 cell count. In a Zambian descriptive necropsy study of 264 children in hospital who died of a respiratory illness before ART, 76 (51%)

infants with HIV aged less than 6 months had evidence of *P jirovecii* pneumonia infection.[26] Where diagnostic facilities were available, *P jirovecii* was found in nearly 10% of children who had not been treated with ART (median age 9 months; range 3–23) who were admitted to hospital with pneumonia in South Africa.[27] In another South African study in which both nasopharyngeal aspirates and induced sputum were collected from 105 children aged less than 2 years who had not been treated with ART, and who were admitted to hospital for a respiratory disease, *P jirovecii* pneumonia was found in 48·6%,[28] with higher rates in those not receiving adequate prophylaxis.

Before ART availability, co-trimoxazole prophylaxis was therefore a highly cost-effective intervention for both adults and children in developing countries, particularly when started early rather than late in disease progression.[29,30]

Panel 1: **Organisms susceptible to co-trimoxazole**

Gram-negative bacteria
- *Escherichia coli*
- *Salmonella* Typhi
- *Salmonella* Typhimurium
- *Salmonella* Paratyphi
- Non-typhi salmonella
- *Shigella* spp
- *Haemophilus influenzae*
- *Neisseria meningitidis*
- *Vibrio cholerae*
- *Yersinia enterocolitica*
- *Klebsiella* spp
- *Achromobacter* spp
- *Acinetobacter* spp
- *Aeromonas hydophila*
- *Alcaligenes* spp
- *Brucella* spp
- *Burkholderia* spp
- *Coxiella burnetii*
- *Proteus mirabilis*
- *Stenotrophomonas maltophilia*
- *Tropheryma whipplei*

Gram-positive bacteria
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
- Group B Streptococcus
- *Staphylococcus aureus*
- Meticillin-resistant *staphylococcus aureus* (MRSA)
- *Staphylococcus epidermidis*
- *Listeria monocytogenes*
- *Actinomyces* spp
- *Nocardia* spp

Mycobacteria
- *Mycobacterium tuberculosis*
- *Mycobacterium fortuitum*
- *Mycobacterium marinum*
- *Mycobacterium kansasii*

Protozoa
- *Plasmodium falciparum*
- *Toxoplasma gondii*
- *Acanthamoeba* spp
- *Cyclospora* spp.
- *Isospora belli*

Fungi
- *Pneumocystis jirovecii*
- *Paracoccidioides brasiliensis*

Susceptibility incorporates in-vitro evidence, case studies, and larger clinical studies.[3,9–13]

Before ART availability, co-trimoxazole prophylaxis was therefore a highly cost-effective intervention for both adults and children in developing countries, particularly when started early rather than late in disease progression.[29,30]

Co-trimoxazole in the ART era

The role of co-trimoxazole in the ART era seems to differ between settings. In developed countries, where infectious disease prevalence is lower and immunisation rates are higher than in developing countries, co-trimoxazole is predominantly used to prevent opportunistic infections in patients with advanced disease. Data from observational studies and small trials suggest that co-trimoxazole can safely be stopped after immune reconstitution with ART. In a randomised trial of co-trimoxazole cessation in 60 Spanish adults taking ART, there were no episodes of *P jirovecii* pneumonia in those discontinuing co-trimoxazole.[31] Similarly, in a European observational cohort of 325 adults stopping co-trimoxazole prophylaxis at a CD4 cell count of at least 350 cells per µL, there were no episodes of *P jirovecii* pneumonia over a median 13 months of follow-up,[32] and in a further European study, there were no cases of toxoplasmosis after discontinuation of co-trimoxazole.[33] In a randomised trial of co-trimoxazole cessation in ART-treated Thai adults with virological suppression but incomplete immune recovery (CD4 cell count <200 cells per µL), only one of 37 patients discontinuing prophylaxis developed *P jirovecii* pneumonia, leading the investigators to conclude that even in this middle-income setting, discontinuation of co-trimoxazole was safe.

In children, the US-based PACTG 1008 trial[34] assessed the discontinuation of co-trimoxazole prophylaxis after immune reconstitution (CD4 cell count ≥20% total lymphocyte count for age >6 years; or CD4 cell count ≥25% for age 2–6 years). There were no occurrences of *P jirovecii* pneumonia during 347 person-years of follow-up, and although a control group was not assessed, the incidence of serious bacterial infections was similar to a historic group of children with HIV, and similar to the background rate in children without HIV.[34] A retrospective analysis of cohorts from the Paediatric European Network for the Treatment of AIDS showed no episodes of *P jirovecii* pneumonia in 335 patient-years after discontinuation of co-trimoxazole in children with adequate immune reconstitution.[34] Paediatric guidelines from the USA and Europe therefore recommend stopping of co-trimoxazole prophylaxis when an adequate

CD4 cell count is achieved after at least 6 months of ART.[35,36]

In developing countries, provision of ART has increased by 20 times since 2003; by the end of 2012, around 9·7 million people in these countries were receiving treatment.[37] A meta-analysis of observational studies reported a 58% (95% CI 39–71%) reduction in early mortality in adults starting ART with co-trimoxazole prophylaxis at CD4 cell counts of 350 cells per μL or less.[3,38] An analysis of expanding co-trimoxazole coverage in developing countries estimated it to be highly cost effective in the first 6 months of ART, at US$146·91 per death averted.[39] Co-trimoxazole prophylaxis also has benefits in adults with less advanced immunodeficiency, reducing WHO stage 3 and 4 disease, severe bacterial infections, and admissions to hospital in those with CD4 cell counts of 350 cells per μL or more.[3,16]

One important benefit for people living in developing countries is the antimalarial protection provided by co-trimoxazole. In two prospective cohorts of adults with HIV in Uganda, co-trimoxazole prophylaxis, ART, and bednets were sequentially introduced over a 4-year period.[12] Malaria incidence substantially reduced after the introduction of co-trimoxazole alone (from 50·8 to 9·0 episodes per 100 person-years); the subsequent addition of ART and bednets further reduced the incidence of malaria to 3·5 and 2·1 episodes per 100 person-years, respectively. In an observational substudy of the DART trial,[40] co-trimoxazole prophylaxis was associated with a 26% reduction of new malarial episodes in current users, which was maintained throughout follow-up (median 4·9 years). In adults with HIV with high CD4 cell counts (≥350 cells per μL), co-trimoxazole prophylaxis has similarly been associated with reductions in malaria in Cote d'Ivoire and Uganda.[16,17,41]

Whether co-trimoxazole prophylaxis can safely be stopped in adults receiving ART has been investigated in several studies. A randomised trial of co-trimoxazole cessation in 836 ART-treated Ugandan adults with CD4 cell counts of more than 200 cells per μL was discontinued after only 4 months because of a significantly increased incidence of diarrhoea (incidence rate ratio [IRR] 1·8, 95% CI 1·3–2·4; p<0·001) and malaria (IRR 32·5, 95% CI 8·6–275; p<0·001) in those who stopped treatment; a post-hoc analysis also showed increased respiratory tract infections in the group who stopped treatment.[42] The early study termination after these results precluded finding out the long-term effects of stopping co-trimoxazole, and raised the possibility that increased infections might have been transient rebound effects.[42] The duration of protection provided by co-trimoxazole after ART initiation was also difficult to establish in the meta-analysis of adult studies, because most had less than 1 year of follow-up.[38] However the DART trial,[40] which had the longest follow-up, showed a survival benefit of co-trimoxazole for the first 72 weeks of ART in a non-randomised analysis, with no effect on mortality thereafter; the benefits of co-trimoxazole were noted across a range of CD4 cell counts.[40] A trial of co-trimoxazole cessation in a malaria-endemic region of western Kenya,[43] in 500 adults with HIV receiving ART for a median of 4·5 years, showed increased morbidity driven entirely by malaria, but no significant differences in pneumonia, diarrhoea, or mortality, between those stopping versus those continuing co-trimoxazole. An ongoing study in Uganda (COSTOP; ISRCTN44723643) is also investigating co-trimoxazole cessation in adults with HIV receiving ART. Therefore, although the duration of protection provided by co-trimoxazole is uncertain, co-trimoxazole seems to provide ongoing benefits to adults receiving long-term ART, despite immune reconstitution, in settings with a high incidence of malaria and bacterial infections.

Children in developing countries receiving long-term ART also benefit from co-trimoxazole prophylaxis. In the open-label Antiretroviral Research for Watoto (ARROW) trial,[8] 758 Ugandan and Zimbabwean children aged more than 3 years, with good CD4 cell counts after a median 2·1 years receiving ART, were randomly assigned to stop or continue co-trimoxazole. The rates of admission to hospital or death were significantly higher in the stop versus continue group (hazard ratio [HR] 1·64, 95% CI 1·14–2·37; p=0·007), because of malaria and other infections (predominantly pneumonia, sepsis, and meningitis), in both Uganda (malaria endemic) and Zimbabwe (not malaria endemic). This effect occurred irrespective of age or CD4 cell count, which emphasises the protection that co-trimoxazole provides against severe bacterial infections even at high CD4 cell counts, by contrast with developed countries.[44] Children in ARROW had sustained protection provided by co-trimoxazole for more than 2 years of follow-up, with no evidence of attenuation over time. Co-trimoxazole also lowered costs, mainly because of reduced hospital admissions.[8]

Tolerability of co-trimoxazole

In the DART trial,[40] during 8128 person-years receiving co-trimoxazole, only 3% of serious adverse events were potentially attributed to this drug. Additionally, prophylaxis with co-trimoxazole was well tolerated in children not receiving ART in the CHAP trial;[6] although neutrophil counts declined in those taking co-trimoxazole, the rate of grade 3 or 4 adverse events (including neutropenia) was similar and very low between the treatment group and the placebo group. Only one child (in the placebo group) developed a grade 3 rash necessitating drug discontinuation in CHAP. In the ARROW trial, although there was a significant increase in both the white cell count and neutrophils in the stop versus continue group, only one child (in the stop group) had a grade 3 or 4 adverse event that was judged to be potentially related to co-trimoxazole, and definitely related to zidovudine.[8] However, neutropenia was reported in adults initiating ART in Côte d'Ivoire, 80% of whom were receiving co-trimoxazole. 118 of 498 adults developed grade 3 or 4 neutropenia, of whom 86 stopped

co-trimoxazole because of persistent neutropenia.[45] Co-trimoxazole has overlapping side-effects with other drugs that are commonly prescribed for individuals with HIV. For example, bone marrow suppression can be caused by antiretroviral drugs such as zidovudine; skin rash (and even Stevens-Johnson syndrome) can occur with non-nucleoside reverse transcriptase inhibitors such as nevirapine; and hepatotoxic effects can occur with antituberculous drugs such as rifampicin and isoniazid. Even within a clinical trial, it can be difficult to ascertain which drug is causative, and a staged approach to drug cessation is often needed.

Co-trimoxazole in women with HIV and exposed infants

Co-trimoxazole prophylaxis has important benefits for pregnant and breastfeeding women with HIV, and their infants. Trimethoprim crosses the placenta and enters breast milk at a concentration equal to the concentration in maternal plasma. Sulfamethoxazole partly crosses into these compartments, meaning that fetuses and infants are substantially exposed to co-trimoxazole during pregnancy and breastfeeding.[46,47] Although there have been concerns about the risks of folate antagonists to a developing fetus, a systematic review undertaken by WHO[48] did not find evidence of increased teratogenicity in the children of pregnant women taking co-trimoxazole, although most studies were of low quality and further prospective surveillance is needed.

Antenatal co-trimoxazole in HIV-infected pregnant women with low CD4 cell counts (<200 cells per μL) was associated with less preterm delivery, reduced neonatal mortality, and a trend towards improved birthweight compared with pregnant women with HIV not taking co-trimoxazole.[49] In a double-blind, placebo-controlled trial, postpartum co-trimoxazole prophylaxis for breastfeeding Zambian women with HIV had no effect on maternal mortality or hospital admissions, although interpretation was limited by a high rate of loss-to-follow-up; however, exploratory analyses showed a trend towards reduced infant mortality in the maternal intervention group (death rate 19·5 with co-trimoxazole [95% CI 12·9–29·3] versus 34·5 with placebo [95% CI 24·4–48·8] per 100 child-years; p=0·1).[50]

In geographical areas with moderate-to-high malaria transmission, WHO recommends intermittent, preventive treatment with antimalarial drugs in pregnancy (IPTp).[51] HIV infection almost doubles the risk of placental malaria,[52] but daily co-trimoxazole prophylaxis reduces this risk[53] and can be used instead of IPTp in pregnant women with HIV.[48] Several randomised trials in western and southern Africa[54–56] and an observational study in Malawi[57] have showed that co-trimoxazole is non-inferior to IPTp in terms of birth outcomes in women with HIV.

Since 2000, WHO has recommended co-trimoxazole prophylaxis for all HIV-exposed infants because of frequent delays in early infant diagnosis and the high risk of *P jirovecii* pneumonia in infected infants. Co-trimoxazole should be started at age 4–6 weeks and continued until HIV infection has been excluded and the child is no longer at risk of infection.[58,59] Because of an increase in prevention of mother-to-child transmission (PMTCT) programmes, the number of HIV-exposed uninfected (HEU) infants is increasing.[60] HEU infants have increased morbidity and mortality compared with unexposed infants,[61] including susceptibility to *P jirovecii* pneumonia.[27,62,63] To investigate the possible protective effects of co-trimoxazole, 185 Ugandan HEU infants, enrolled aged between 6 weeks and 9 months, were randomly assigned upon cessation of breastfeeding to either stop or continue co-trimoxazole until age 2 years.[64] Although rates of diarrhoea, pneumonia, hospital admission, and mortality were unaffected, the incidence of malaria was reduced by 39% in the continue co-trimoxazole group (IRR 0·61, 95% CI 0·46–0·81; p=0·001), despite a high prevalence of antifolate resistance. An observational analysis of infants before and after co-trimoxazole introduction in the BAN trial[65] also showed reduced malaria but no effect on severe illness, death, weight-for-age, or anaemia.

Some researchers argue that co-trimoxazole for HEU infants might be detrimental. An observational South African study showed no protection against pneumonia, and a possible increase in diarrhoea in HEU infants receiving co-trimoxazole prophylaxis.[66] Co-trimoxazole can cause skin rashes, gastrointestinal disturbances, and neutropenia, particularly if infants are also taking ART.[67,68] However, a study of 1705 HEU infants in Botswana reported a low frequency of severe anaemia and neutropenia between ages 1 to 6 months, providing reassurance that prolonged co-trimoxazole is generally not associated with severe haematological toxicity.[69] Coutsoudis and colleagues[68] have, however, argued that the risks of co-trimoxazole prophylaxis might outweigh the benefits for HEU infants, particularly because HIV transmission rates within well functioning prevention of mother-to-child transmission (PMTCT) programmes are low, and evidence for benefit of co-trimoxazole in HIV-uninfected children is weak.[68] A laboratory study of infants in the BAN trial[70] proposed that co-trimoxazole could actually increase the risk of mother-to-child HIV transmission, although reasons for this are unclear. HIV-exposed infants receiving co-trimoxazole had higher concentrations of plasma lipopolysaccharide than those not receiving co-trimoxazole (p=0·004), leading the investigators to speculate that changes to the intestinal microbiota after long-term antibiotic use led to gut damage (with associated microbial translocation) and increased risk of HIV transmission.[70] However, co-trimoxazole was not randomised in this trial, which enrolled infants before and after introduction of prophylaxis, and there was no direct assessment of intestinal damage or microbiota composition, so further studies are needed to better understand this finding.

Widespread co-trimoxazole prophylaxis is also associated with increased community antimicrobial resistance. A longitudinal cohort study of Zambian infants showed an initial decrease in nasopharyngeal pneumococcal colonisation in HEU infants taking co-trimoxazole; however, within 6 weeks there was increased colonisation with co-trimoxazole-resistant pneumococci compared with HIV-unexposed infants (relative risk 3·2, 95% CI 1·3–7·8).[71] In a substudy of the CHAP trial,[72] children with HIV randomly assigned to co-trimoxazole paradoxically had higher rates of pneumococcal carriage and higher rates of co-trimoxazole resistance among *Streptococcus pneumoniae* and *Haemophilus influenzae* isolates than with placebo; but despite increased resistance, co-trimoxazole reduced morbidity and mortality from invasive bacterial disease.[6]

To assess the benefits and risks of co-trimoxazole prophylaxis for HIV-exposed uninfected infants, a trial in Botswana is randomly assigning more than 3000 HEU infants to co-trimoxazole or placebo until age 15 months (ClinicalTrials identifier NCT01229761). The primary outcome is survival at age 18 months; secondary endpoints include morbidity and mortality at 18 months, and safety of co-trimoxazole. A second trial of co-trimoxazole prophylaxis in breastfed HEU infants, with primary outcomes of morbidity (diarrhoea and pneumonia) and all-cause mortality up to age 54 weeks, is recruiting in Durban, South Africa (ClinicalTrials identifier PACTR201311000621110); neither trial is taking place in a malaria-endemic area.

Guidelines for co-trimoxazole for people living with HIV

Guidelines have generally shifted over time, from use of co-trimoxazole as a pre-ART intervention for people with advanced HIV disease to universal, adjunctive, co-trimoxazole prophylaxis at ART initiation as part of a package of HIV care. Even in those not yet eligible for ART, provision of free co-trimoxazole improves retention in care.[73] WHO guidelines were updated in 2014 to recommend long-term co-trimoxazole prophylaxis for adults (including pregnant women), irrespective of disease stage or CD4 cell count in geographical areas with a high prevalence of malaria or severe bacterial infections, or both, although initiation and discontinuation criteria are still provided for other settings.[48] Co-trimoxazole should be initiated for all infants, children, and adolescents, irrespective of disease stage or use of ART; similar to adults, prophylaxis should continue long term in settings of high malaria or severe bacterial infections, or both.

Implementation of these guidelines is challenging because co-trimoxazole coverage is low. Of 4050 HIV-infected adults attending 19 clinics in the Asia-Pacific region between 2003 and 2009, around a third were not taking co-trimoxazole; these patients had more than ten times higher mortality than those receiving prophylaxis.[74]

Globally, WHO estimated 71% co-trimoxazole coverage in 2010, but acknowledged that these data were probably inaccurate.[75] Only 23% of HEU infants received co-trimoxazole in 2010,[75] because of difficulties in follow-up and challenges with drug forecasting, procurement, and supply. Co-trimoxazole scale-up therefore provides a good example of how research evidence does not necessarily translate into programmatic changes, which might be highly dependent on the political and economic situation in a country.[76] Effective implementation of new guidelines will need strengthening of drug supply management systems to prevent stock-outs, linkage with other programmes, better community awareness, sensitisation and training of health-care workers, and free provision of co-trimoxazole. Expansion of co-trimoxazole provision should also be accompanied by strategic surveillance for toxic effects and antimicrobial resistance.

Antimicrobial benefits despite high-level resistance

Bacterial resistance to co-trimoxazole is predominantly mediated by efflux pumps and mutated target enzymes. The mutated enzymes are transferable via plasmid-encoded changes in dihydrofolate reductase.[9] Antimicrobial resistance started to emerge after greater empirical use of

	Resistance prevalence	Country or region	HIV-positive participants	Co-trimoxazole prophylaxis
Escherichia coli[77–83]	56–91%	Africa: Côte d'Ivoire, Kenya, South Africa, Uganda	Mixed	Mixed
E coli[84]	64%	Laos	Unknown (<1%)	None
Group B streptococcus[78]	15%	Sub-Saharan Africa and Asia	Not stated	Not stated
Haemophilus influenzae[78,81,85–88]	33–98%	Africa: South Africa, Kenya, Uganda	Mixed	Mixed
Neisseria meningitidis[78]	62%	Sub-Saharan Africa and Asia	Not stated	Not stated
Non-Typhi salmonella[17,77,78,82,83,87,89,90]	0–85%	Africa: Côte d'Ivoire, Kenya, Malawi, Uganda	Mixed	Mixed
Non-Typhi salmonella[84]	11%	Laos	Unknown (<1%)	None
Plasmodium falciparum[64,80,91–93]	13–100%	Africa: Kenya, Uganda, Mali	Mixed	Mixed
Salmonella Typhi[78,82]	11–27%	Africa	Mixed	Unknown
Shigella spp[17,77,83,87]	84–100%	Africa: Uganda, Côte d'Ivoire	Mixed	Mixed
S aureus[77,78,81,82,85,94]	25–100%	Africa: Côte d'Ivoire, South Africa, Uganda,	Mixed	Mixed
S aureus[84]	22%	Laos	Unknown (<1%)	None
Streptococcus pneumoniae[71,77,78,80–82,84,85,87,88,90,94–97]	22–99%	Africa: Côte d'Ivoire, South Africa, Malawi, Zambia, Kenya, Uganda	Mixed	Mixed
Streptococcus pneumoniae[84]	80%	Laos	Unknown (<1%)	None

Table: **Co-trimoxazole resistance in common bacterial isolates from developing countries**

co-trimoxazole in the 1970s.[9] With more widespread use during the HIV epidemic, further increases in microbial co-trimoxazole resistance were noted, and rates are now extremely high in many settings (table and appendix).

See Online for appendix

Despite high resistance rates, co-trimoxazole continues to reduce morbidity and mortality from bacterial infections,[16,17,98] for reasons that are unclear. In Zambia, background resistance was 61% among *S pneumoniae* isolates,[71] yet the predominant effect of co-trimoxazole in the CHAP trial was reduction in pneumonia.[20] In Uganda, despite a rise in diarrhoeal-pathogen resistance to 83% after co-trimoxazole introduction, significant reductions in diarrhoea were seen (HR 0·65, 95% CI 0·53–0·81; p<0·0001).[15] Despite high resistance rates, co-trimoxazole could still have sufficient antimicrobial activity to prevent severe disease, particularly because it is concentrated intracellularly.[47] Furthermore, its activity against non-bacterial pathogens could have been underestimated.[8, 99]

Mechanism of action of co-trimoxazole: beyond antimicrobial properties

Co-trimoxazole has been known for several decades as a unique compound with important properties beyond its antimicrobial effects, and these mechanisms could be crucial to understand some of its clinical benefits (figure 1). The immunomodulatory properties of co-trimoxazole were first suggested in a study by Ghilchik and colleagues in 1970.[106] They noted that trimethoprim has a pyrimidine ring that is structurally similar to the immunosuppressive agent azathioprine, and they showed that giving intramuscular trimethoprim prolonged the survival of skin grafts transplanted from brown to white mice, with graft survival times comparable to those achieved using azathioprine.[106] In the presence of a folinate analogue, the effect was no longer sustained, leading the investigators to make two inferences: first, that the immunosuppressive action of trimethoprim was derived from the same antifolate properties that confer antimicrobial activity; and second, that this occurs specifically through the inhibition of T cells, which are needed for allograft rejection. Soon after this discovery, other researchers confirmed that co-trimoxazole can directly modulate lymphocyte function. Lymphocytes from 25 healthy adult volunteers were cultured with phytohaemagglutinin (a T-cell mitogen) in the presence of trimethoprim, sulfamethoxazole, or co-trimoxazole. Decreased thymidine uptake was noted in cells from 15 (60%) of the volunteers, with the greatest suppression of proliferation in lymphocytes incubated with co-trimoxazole, compared with either of its constituent drugs.[107] In a study of 40 individuals vaccinated against tetanus, half received 4 days of co-trimoxazole (480 mg twice a day) immediately after vaccination, and the other half received no antibiotics. Antitetanus antibody titres 4 and 5 weeks after vaccination were significantly lower in the treated participants compared with the untreated participants. The results from these studies suggest that co-trimoxazole is able to prevent lymphocyte proliferation, perhaps through inhibition of the human folate reductase enzyme.

Co-trimoxazole could conversely enhance innate immune function by increasing the bactericidal activity of neutrophils.[5,108–110] An in-vitro study of alveolar macrophage function in a few adults with advanced HIV infection showed enhanced phagocytosis and killing of *Staphylococcus aureus* in those taking co-trimoxazole, compared with untreated individuals.[111] However, there is some inconsistency between studies. For example, inhibition of both lymphocyte and neutrophil activity in one clinical study was evident only at high drug concentrations in vitro and was not found in cells taken from three participants after oral dosing (960 mg twice a day) of co-trimoxazole.[112] Moreover, children treated with co-trimoxazole for urinary tract infections had no differences in antibacterial cellular or humoral immune responses compared with children treated with other antibiotics, and an investigation of the immunoregulatory properties of co-trimoxazole in guinea pigs showed no effect on either interleukin 1 or tumour necrosis factor α production from alveolar macrophages.[113,114]

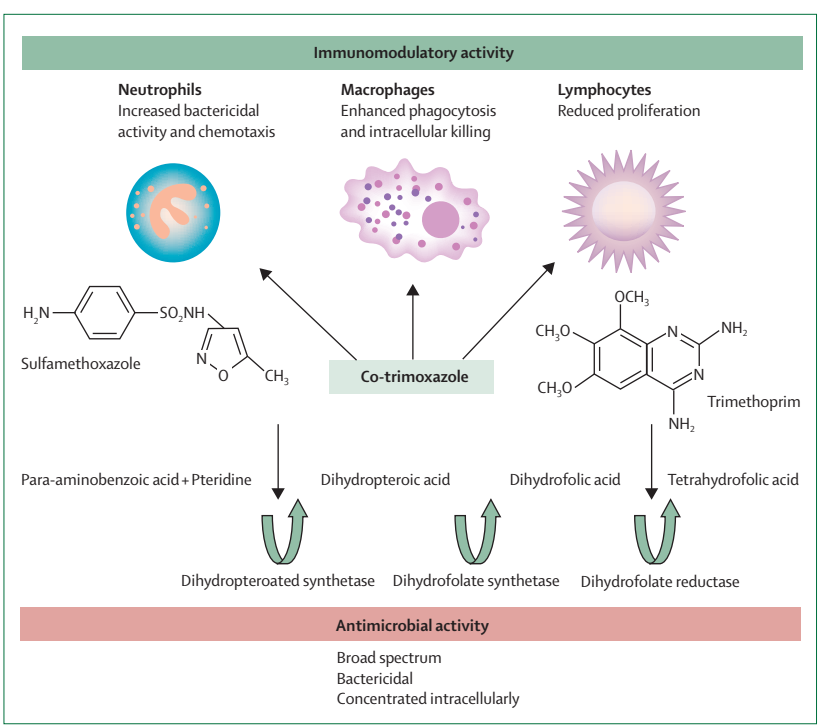

Figure 1: **Mechanisms of action of co-trimoxazole**
Co-trimoxazole, a fixed-dose combination of trimethoprim and sulfamethoxazole, has both immunomodulatory and antimicrobial properties. Some in-vitro evidence suggests that co-trimoxazole can modulate both innate and adaptive immune cells, with increased bactericidal activity and chemotaxis of neutrophils,[5,100–102] enhanced phagocytosis and intracellular killing by macrophages[103] and reduced proliferation of lymphocytes.[104,105] Antimicrobial activity of co-trimoxazole occurs through the sequential blockade of two enzymes in the folate biosynthetic pathway: inhibition of dihydropteroate synthetase by sulfamethoxazole, and inhibition of dihydrofolate reductase by trimethoprim. The compound therefore has broad-spectrum bactericidal activity, which might be enhanced by high intracellular concentrations of co-trimoxazole.[59]

Several clinical studies of rheumatological and autoimmune conditions support the postulation of immunomodulatory and anti-inflammatory effects of co-trimoxazole.[104] Two small, non-randomised studies that assessed adjunctive therapy in rheumatoid arthritis showed improved clinical function and reduced inflammation in patients treated with co-trimoxazole or its component sulfamethoxazole.[100,105] Co-trimoxazole has also been used to prevent relapses in Wegener's granulomatosis.[101,102] Although this effect has been partly attributed to its antibacterial properties, because *S aureus* can trigger relapses,[103] co-trimoxazole could also modulate T-cell activity or reduce free-radical production through its anti-inflammatory properties.[101,115] Co-trimoxazole has also been used with variable effects in the management of inflammatory bowel disease and temporal arteritis.[116,117] Therefore, there is reasonable evidence that co-trimoxazole has mechanisms of action beyond its antimicrobial effects, but its immunomodulatory properties require better in-vitro characterisation and further clinical assessment in randomised trials of chronic inflammatory diseases.

Expanding roles for co-trimoxazole in developing countries?

The anti-inflammatory potential of co-trimoxazole might be especially useful in developing countries, where several diseases, such as HIV infection and malnutrition, are characterised by recurrent infections and chronic inflammation.[118,119] Some of the benefits of co-trimoxazole in individuals with HIV could therefore arise from reductions in immune system activation.[8,40,120] In the ARROW trial, children who were randomly assigned to discontinue co-trimoxazole had more anaemia (including potentially life-threatening anaemia) than children continuing co-trimoxazole—this effect was not simply due to increased malaria.[8] Children who were not receiving ART who were randomly assigned to co-trimoxazole in the CHAP trial had a four times greater increase in haemoglobin than those taking placebo and a slower decrease in weight and height.[120] Similarly, there was a trend towards greater weight (but not height) in children in ARROW who continued co-trimoxazole.[8] Although growth failure and anaemia in children with HIV have multifactorial causes, immune activation is probably a major contributor and co-trimoxazole could partly work through a reduction in chronic inflammation. Consistent with this concept, children who were randomly assigned to discontinue co-trimoxazole in ARROW showed a transient rise in several inflammatory biomarkers (interleukin 6, soluble CD14, and tumour necrosis factor α), and a sustained rise in C-reactive protein which persisted for more than 2 years after stopping co-trimoxazole.[121]

More mechanistic studies are needed to investigate whether co-trimoxazole has anti-inflammatory benefits in individuals with HIV; however, plausibly these could occur either directly, through effects on innate and adaptive immune cells, or indirectly by attenuating microbial translocation across an impaired intestinal barrier. Simian immunodeficiency virus-infected sooty mangabeys had reduced plasma concentrations of lipopolysaccharide (a marker of microbial translocation) when treated with a bowel-sterilising antibiotic regimen, and co-trimoxazole has been used previously in the treatment of small intestinal bacterial overgrowth with metronidazole.[122,123] In the DART trial,[40] reduced microbial translocation could have contributed to the lower mortality seen in adults with HIV receiving co-trimoxazole.

Whether co-trimoxazole might similarly reduce mortality and improve growth in children without HIV is unknown, but seems plausible. A systematic review[124] of pooled data from ten randomised trials of various antibiotics in prepubertal children in developing countries showed significant increases in both weight and height, with effects postulated to be due to treatment of subclinical infections and modulation of intestinal microbial populations.[124] Co-trimoxazole has also been shown to improve anthropometric indicators (body-mass index, arm muscle circumference, and percentage of fat mass) in malnourished adults with HIV in Côte d'Ivoire.[125] However, the greatest benefits are likely to be in children aged less than 2 years for whom a window of opportunity exists to improve linear growth and long-term neurodevelopmental outcomes during the first 1000 days.

For more on the **first 1000 days** see http://www.thousanddays.org

Children living in impoverished conditions frequently have compromised intestinal barrier function.[126] Enteropathy can have many causes in this setting, including environmental enteric dysfunction, persistent diarrhoea, micronutrient deficiencies, and severe acute malnutrition, which overlap and interact to drive morbidity and mortality in young children.[127] Interest is increasing in the potential for antibiotics such as co-trimoxazole to affect the interplay between enteropathy, malnutrition, and morbidity.[118] In a double-blind, randomised, placebo-controlled trial in Bangladesh, children with persistent diarrhoea had reduced stool output and higher recovery rates within 7 days of starting co-trimoxazole.[128] Children admitted to hospital with severe acute malnutrition frequently have invasive bacterial infections.[129] However, WHO guidelines recommend broad-spectrum antimicrobials because several studies of children with complicated severe acute malnutrition have shown that bacteraemia frequently occurs with organisms that are resistant to co-trimoxazole.[130–132] A community-based trial in Malawian children with uncomplicated, severe acute malnutrition showed lower mortality in those randomly assigned to antibiotics (either amoxicillin or cefdinir), compared with placebo, despite no clinical signs of infection.[133] In view of the emerging role of the microbiota in the pathogenesis of malnutrition, antibiotics could plausibly

modulate intestinal microbial populations and confer benefits beyond a simple reduction in invasive bacterial infections.[134] A large clinical trial in Kenya (NCT00934492) is investigating the effect of co-trimoxazole after the stabilisation of children admitted to hospital for severe acute malnutrition.[118,135] Children without HIV were randomly assigned to receive co-trimoxazole or placebo for 6 months after their discharge from hospital, with a primary endpoint of survival at 1 year. Secondary endpoints in this trial include growth, microbial resistance, and markers of inflammation and immune function. Another large African trial, Transfusion and Treatment of Severe Anaemia in African Children (TRACT, ISRCTN84086586), includes co-trimoxazole as an adjunctive treatment after blood transfusion in nearly 4000 children with life-threatening anaemia. Children have an ongoing high risk of mortality and hospital readmission after treatment for severe anaemia, and as part of a factorial design, interventions include a 3 month course of co-trimoxazole as a strategy to reduce infectious morbidity and mortality in this high-risk group.

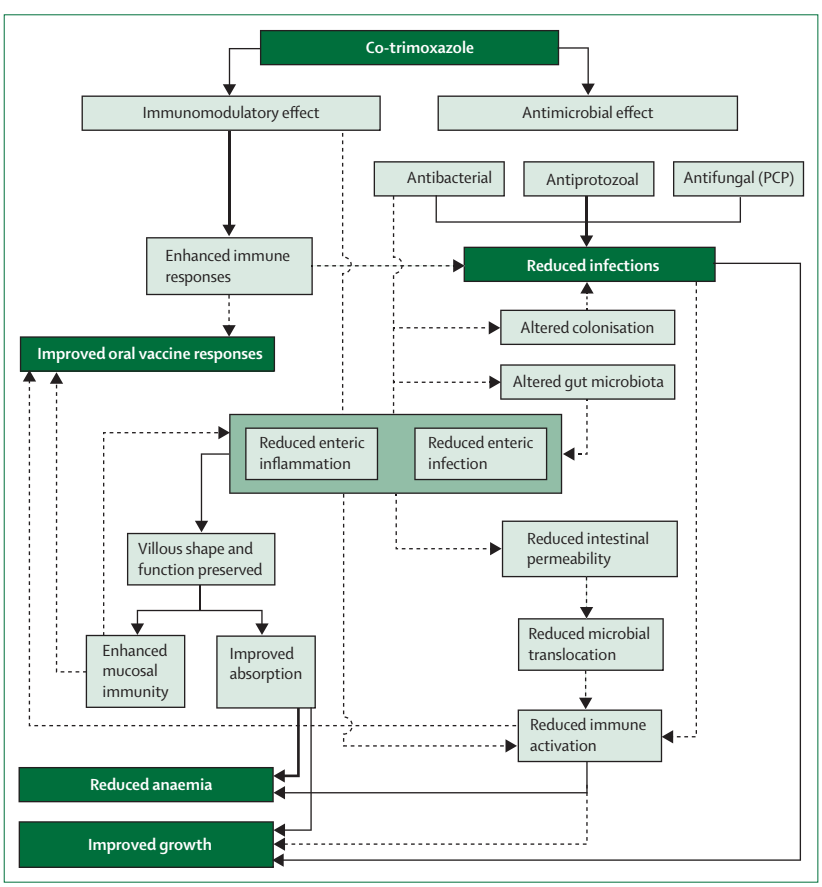

***Figure 2*: Possible pathways for the actions of co-trimoxazole**
Co-trimoxazole might plausibly act through several interacting biological pathways. The antimicrobial properties of co-trimoxazole reduce the incidence and severity of infections, both directly, and possibly indirectly by altering nasopharyngeal colonisation and composition of the intestinal microbiota. Modulation of the intestinal microbiota might prevent the structural and functional gut changes that characterise environmental enteric dysfunction (EED). Preservation of villous architecture could improve absorption of nutrients, which leads directly to better growth, and might enhance mucosal immune responses. EED is also characterised by increased intestinal permeability, which enables microbial translocation to occur, driving a state of chronic systemic inflammation. Known effects of co-trimoxazole are indicated by bold lines, mechanisms for which there are some published data (as discussed in the text) are shown by solid lines. Speculative mechanisms that are based on biological plausibility, but for which there are no published data, are shown in dashed lines. PCP= Pneumocystis pneumonia.

Therefore, co-trimoxazole could operate through several interlinked pathways: direct reduction of opportunistic infections; changes in nasopharyngeal colonisation; modulation of the intestinal microbiota, leading to amelioration of enteropathy and reduction of microbial translocation; direct enhancement of immune responses; and a reduction in systemic inflammation (figure 2). These multiple pathways could partly explain the broad benefits of co-trimoxazole in patients in developing countries, despite high rates of microbial resistance, and they suggest other plausible benefits of co-trimoxazole that have not yet been investigated, such as improvements in oral vaccine responses.

In both developed and developing countries, co-trimoxazole use has resurged for a wide range of infections, particularly for those usually deemed difficult to treat, such as melioidosis,[136] brucellosis (in younger children),[137] *Stenotrophomonas maltophilia*,[138] *Burkholderia cepacia*[139] in immunocompromised patients, and Q fever (although the evidence for long-term treatment during pregnancy is conflicting).[140,141] Co-trimoxazole is also a recognised treatment for paracoccidioidomycosis.[13] Moreover, in-vitro studies have suggested that co-trimoxazole has activity against *Mycobacterium tuberculosis*,[142,143] particularly the sulphonamide component of the drug.[143] This suggestion is supported by a recent report of adults with HIV followed up for 20 years within the Swiss HIV Cohort, for whom cumulative co-trimoxazole exposure reduced the risk of incident tuberculosis, particularly in individuals not receiving ART.[144] However, not all studies have shown a protective effect of co-trimoxazole against tuberculosis.[16,40,145] Importantly, the use of co-trimoxazole could extend to the treatment of multidrug-resistant tuberculosis[146] and meticillin-resistant *S aureus*, with susceptibility seeming to differ by geographical region.[147–150]

Conclusions

Co-trimoxazole provides important benefits for adults and children in developing countries, reducing morbidity and mortality particularly in the setting of HIV infection, despite high levels of pathogen resistance. Recent data emphasise the long-term benefits of continuation of co-trimoxazole in patients receiving ART. There is both optimism and scepticism about expanding the use of co-trimoxazole in populations without HIV in developing countries. Its unique antimicrobial and immunomodulatory properties could provide benefits beyond a simple reduction in infections, and therefore interest is increasing in adjunctive use of co-trimoxazole for susceptible populations, such as children recovering from malnutrition or severe anaemia. Whether co-trimoxazole has a role in modulating the microbiota, reducing

Panel 2: Future research directions for co-trimoxazole

- Investigate how co-trimoxazole reduces morbidity and mortality in settings of high-microbial resistance
- Explore the immunomodulatory properties of co-trimoxazole with contemporary laboratory methods
- Investigate the effect of co-trimoxazole on the intestinal microbiota, gut barrier function, and microbial translocation
- Assess the role of co-trimoxazole in the reduction of morbidity and mortality and improvement of growth in HIV-exposed children without infection and HIV-unexposed children in developing countries
- Explore the effect of antenatal co-trimoxazole in the reduction of adverse birth outcomes and improvement of fetal growth in pregnant women with or without HIV in developing countries
- With the expansion of co-trimoxazole prophylaxis for adults and children with HIV, assess the duration of protection and tolerability of long-term co-trimoxazole and undertake surveillance for toxic effects and microbial resistance.
- Assess the benefits of long-term co-trimoxazole for individuals with HIV receiving antiretroviral therapy in developed countries—eg, a reduction in bacterial infections, immune activation, and non-AIDS morbidity and mortality
- Define the role of co-trimoxazole in the prevention and treatment of tuberculosis, including multidrug-resistant tuberculosis

Search strategy and selection criteria

We searched PubMed using the terms "trimethoprim-sulfamethoxazole combination", "trimethoprim-sulfamethoxazole", "CTX", "septrin", "cotrimoxazole", and"co-trimoxazole" for English-language papers published between Jan 1, 1969, and Jun 26, 2014. We screened titles and abstracts of papers, and reviewed the reference lists of selected articles and relevant conference proceedings.

inflammation, or promoting growth during the first 1000 days of a child's life in developing countries warrants further exploration (panel 2), but more widespread use of antibiotics generates concerns.[151] The number of HIV-exposed children who qualify for co-trimoxazole has increased hugely, because effective PMTCT regimens reduce vertical HIV transmission. Additionally, the risks of side-effects, increasing antimicrobial resistance, and increased costs need to be balanced against the potential benefits of wider use of co-trimoxazole, and evidence from ongoing trials is awaited. Further studies are needed to better understand the mechanisms through which co-trimoxazole reduces morbidity and mortality so that we can facilitate judicious expansion of co-trimoxazole to populations who are likely to benefit from this well tolerated and affordable intervention.

Contributors

AJP, ASW, and DMG had the original idea for the review. JAC undertook the literature search. JAC, FF, and AJP wrote the first draft of the manuscript (JAC and FF contributed equally to this manuscript). ASW and DMG helped with data interpretation and critically revised the manuscript with AJP.

Declaration of interests

AJP is a member of the WHO Guidelines Review Committee on co-trimoxazole prophylaxis for HIV-infected adults and children. AJP is funded by the Wellcome Trust (093768/Z/10/Z). FF is funded by the Medical Research Council (MR/K023535/1). All other authors declare no competing interests.

References

1 Anon. Septrin and bactrim. A combination of trimethoprim and sulphamethoxazole. *Drug Ther Bull* 1969; **7:** 13–15.
2 Wolff LJ, Baehner RL. Delayed development of pneumocystis pneumonia following administration of short-term high-dose trimethoprim-sulfamethoxazole. *Am J Dis Child* 1978; **132:** 525–26.
3 Hughes WT. Trimethoprim-sulfamethoxazole therapy for *Pneumocystis carinii* pneumonitis in children. *Rev Infect Dis* 1982; **4:** 602–07.
4 Ruskin J, LaRiviere M. Low-dose co-trimoxazole for prevention of *Pneumocystis carinii* pneumonia in human immunodeficiency virus disease. *Lancet* 1991; **337:** 468–71.
5 Emmanouilides CE, Lianou PE, Bassaris HP, Papavassiliou JT. Trimethoprim, sulphamethoxazole, bacterial adhesion and polymorphonuclear leucocyte function. *J Antimicrob Chemother* 1990; **26**: 803–12.
6 Chintu C, Bhat GJ, Walker AS, et al. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. *Lancet* 2004; **364:** 1865–71.
7 Lindemulder S, Albano E. Successful intermittent prophylaxis with trimethoprim/sulfamethoxazole 2 days per week for *Pneumocystis carinii* (jiroveci) pneumonia in pediatric oncology patients. *Pediatrics* 2007; **120:** e47–51.
8 Bwakura-Dangarembizi M, Kendall L, Bakeera-Kitaka S, et al. A randomized trial of prolonged co-trimoxazole in HIV-infected children in Africa. *N Engl J Med* 2014; **370:** 41–53.
9 Masters PA, O'Bryan TA, Zurlo J, Miller DQ, Joshi N. Trimethoprim-sulfamethoxazole revisited. *Arch Intern Med* 2003; **163:** 402–10.
10 Brumfitt W, Hamilton-Miller JM. Limitations of and indications for the use of co-trimoxazole. *J Chemother* 1994; **6:** 3–11.
11 Goldberg E, Bishara J. Contemporary unconventional clinical use of co-trimoxazole. *Clin Microbiol Infect* 2012; **18:** 8–17.
12 Mermin J, Ekwaru JP, Liechty CA, et al. Effect of co-trimoxazole prophylaxis, antiretroviral therapy, and insecticide-treated bednets on the frequency of malaria in HIV-1-infected adults in Uganda: a prospective cohort study. *Lancet* 2006; **367:** 1256–61.
13 Cavalcante Rde S, Sylvestre TF, Levorato AD, de Carvalho LR, Mendes RP. Comparison between itraconazole and cotrimoxazole in the treatment of paracoccidiodomycosis. *PLoS Negl Trop Dis* 2014; **8:** e2793.
14 Rigaud M, Pollack H, Leibovitz E, et al. Efficacy of primary chemoprophylaxis against *Pneumocystis carinii* pneumonia during the first year of life in infants infected with human immunodeficiency virus type 1. *J Pediatr* 1994; **125:** 476–80.
15 Stansell JD, Osmond DH, Charlebois E, et al. Predictors of *Pneumocystis carinii* pneumonia in HIV-infected persons. Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med* 1997; **155:** 60–66.
16 Anglaret X, Chene G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet* 1999; **353:** 1463–68.
17 Mermin J, Lule J, Ekwaru JP, et al. Effect of co-trimoxazole prophylaxis on morbidity, mortality, CD4-cell count, and viral load in HIV infection in rural Uganda. *Lancet* 2004; **364:** 1428–34.
18 Wiktor SZ, Sassan-Morokro M, Grant AD, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. *Lancet* 1999; **353:** 1469–75.

19 Badri M, Ehrlich R, Wood R, Maartens G. Initiating co-trimoxazole prophylaxis in HIV-infected patients in Africa: an evaluation of the provisional WHO/UNAIDS recommendations. *AIDS* 2001; **15:** 1143–48.

20 Mulenga V, Ford D, Walker AS, et al. Effect of cotrimoxazole on causes of death, hospital admissions and antibiotic use in HIV-infected children. *AIDS* 2007; **21:** 77–84.

21 Abouya YL, Beaumel A, Lucas S, Dago-Akribi A, Coulibaly G, N'Dhatz M, et al. *Pneumocystis carinii* pneumonia. An uncommon cause of death in African patients with acquired immunodeficiency syndrome. *Am Rev Respir Dis* 1992; **145:** 617–20.

22 Kamanfu G, Mlika-Cabanne N, Girard PM, et al. Pulmonary complications of human immunodeficiency virus infection in Bujumbura, Burundi. *Am Rev Respir Dis* 1993; **147:** 658–63.

23 Batungwanayo J, Taelman H, Lucas S, et al. Pulmonary disease associated with the human immunodeficiency virus in Kigali, Rwanda. A fiberoptic bronchoscopic study of 111 cases of undetermined etiology. *Am J Respir Crit Care Med* 1994; **149:** 1591–96.

24 Atzori C, Bruno A, Chichino G, Gatti S, Scaglia M. *Pneumocystis carinii* pneumonia and tuberculosis in Tanzanian patients infected with HIV. *Trans R Soc Trop Med Hyg* 1993; **87:** 55–56.

25 Lucas SB, Hounnou A, Peacock C, et al. The mortality and pathology of HIV infection in a west African city. *AIDS* 1993; **7:** 1569–79.

26 Chintu C, Mudenda V, Lucas S, et al. Lung diseases at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study. *Lancet* 2002; **360:** 985–90.

27 Zar HJ, Dechaboon A, Hanslo D, Apolles P, Magnus KG, Hussey G. *Pneumocystis carinii* pneumonia in South African children infected with human immunodeficiency virus. *Pediatr Infect Dis J* 2000; **19:** 603–07.

28 Ruffini DD, Madhi SA. The high burden of *Pneumocystis carinii* pneumonia in African HIV-1-infected children hospitalized for severe pneumonia. *AIDS* 2002; **16:** 105–12.

29 Yazdanpanah Y, Losina E, Anglaret X, Goldie SJ, et al. Clinical impact and cost-effectiveness of co-trimoxazole prophylaxis in patients with HIV/AIDS in Cote d'Ivoire: a trial-based analysis. *AIDS* 2005; **19:** 1299–308.

30 Ryan M, Griffin S, Chitah B, et al. The cost-effectiveness of cotrimoxazole prophylaxis in HIV-infected children in Zambia. *AIDS* 2008; **22:** 749–57.

31 Hudson CP, Roach T. Co-trimoxazole in HIV-1 infection. *Lancet* 1999; **354:** 333.

32 Ledergerber B, Mocroft A, Reiss P, et al. Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection who have a response to antiretroviral therapy. *N Engl J Med* 2001; **344:** 168–74.

33 Mussini C, Pezzotti P, Govoni A, et al. Discontinuation of primary prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type I-infected patients: the changes in opportunistic prophylaxis study. *J Infect Dis* 2000; **181:** 1635–42.

34 Urschel S, Ramos J, Mellado M, et al. Withdrawal of *Pneumocystis jirovecii* prophylaxis in HIV-infected children under highly active antiretroviral therapy. *AIDS* 2005; **19:** 2103–08.

35 PENTA Steering Committee, Welch S, Sharland M, et al. PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. *HIV Med* 2009; **10:** 591–613.

36 Panel on opportunistic infections in HIV-exposed and HIV-infected Children. Guidelines for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children. US Department of Health and Human Services, Nov 6, 2013. http://aidsinfo.nih.gov/contentfiles/lvguidelines/oi_guidelines_pediatrics.pdf (accessed July 8, 2014).

37 UNAIDS. UNAIDS report on the global AIDS epidemic 2013. Nov, 2013. http://www.unaids.org/en/resources/campaigns/globalreport2013/globalreport/ (accessed May 25, 2014).

38 Suthar AB, Granich R, Mermin J, Van Rie A. Effect of cotrimoxazole on mortality in HIV-infected adults on antiretroviral therapy: a systematic review and meta-analysis. *Bull World Health Organ* 2012; **90:** 128C–38C.

39 Abimbola TO, Marston BJ. The cost-effectiveness of cotrimoxazole in people with advanced HIV infection initiating antiretroviral therapy in sub-Saharan Africa. *J Acquir Immune Defic Syndr* 2012; **60:** e8–e14.

40 Walker AS, Ford D, Gilks CF, et al. Daily co-trimoxazole prophylaxis in severely immunosuppressed HIV-infected adults in Africa started on combination antiretroviral therapy: an observational analysis of the DART cohort. *Lancet* 2010; **375:** 1278–86.

41 Watera C, Todd J, Muwonge R, et al. Feasibility and effectiveness of cotrimoxazole prophylaxis for HIV-1-infected adults attending an HIV/AIDS clinic in Uganda. *J Acquir Immune Defic Syndr* 2006; **42:** 373–78.

42 Campbell JD, Moore D, Degerman R, et al. HIV-infected ugandan adults taking antiretroviral therapy with CD4 counts >200 cells/muL who discontinue cotrimoxazole prophylaxis have increased risk of malaria and diarrhea. *Clin Infect Dis* 2012; **54:** 1204–11.

43 Polyak CS, Yuhas K, Benson S, Khaemba M, Walson J, Richardson B, et al. Cotrimoxazole prophylaxis discontinuation among ART-treated adults: a randomised non-inferiority trial. 21st Conference on Retroviruses and Opportunistic Infections; Boston, MA, USA; March 3–6, 2014. Abstract 98.

44 Nachman S, Gona P, Dankner W, et al. The rate of serious bacterial infections among HIV-infected children with immune reconstitution who have discontinued opportunistic infection prophylaxis. *Pediatrics* 2005; **115:** e488–94.

45 Moh R, Danel C, Sorho S, et al. Haematological changes in adults receiving a zidovudine-containing HAART regimen in combination with cotrimoxazole in Côte d'Ivoire. *Antivir Ther* 2005; **10:** 615–24.

46 Reid DW, Caille G, Kaufmann NR. Maternal and transplacental kinetics of trimethoprim and sulfamethoxazole, separately and in combination. *Can Med Assoc J* 1975; **112:** 67–72.

47 Wilkinson PJ, Reeves DS. Tissue penetration of trimethoprim and sulphonamides. J *Antimicrob Chemother* 1979; **5:** 159–68.

48 WHO 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. March, 2014. http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_march2014/en/ (accessed May 25, 2014).

49 Walter J, Mwiya M, Scott N, et al. Reduction in preterm delivery and neonatal mortality after the introduction of antenatal cotrimoxazole prophylaxis among HIV-infected women with low CD4 cell counts. *J Infect Dis* 2006; **194:** 1510–18.

50 Nunn AJ, Mwaba PB, Chintu C, et al. Randomised, placebo-controlled trial to evaluate co-trimoxazole to reduce mortality and morbidity in HIV-infected post-natal women in Zambia (TOPAZ). *Trop Med Int Health* 2011; **16:** 518–26.

51 WHO. Updated WHO policy recommendation: intermittent preventive treatment of malaria in pregnancy using sulfadoxine-pyrimethamine (IPTp-SP). October, 2012. http://www.who.int/malaria/publications/atoz/who_iptp_sp_policy_recommendation/en/ (accessed on May 25, 2014).

52 ter Kuile FO, Parise ME, Verhoeff FH, et al. The burden of co-infection with human immunodeficiency virus type 1 and malaria in pregnant women in sub-saharan Africa. *Am J Trop Med Hyg* 2004; **71:** 41–54.

53 Manyando C, Njunju EM, D'Alessandro U, Van Geertruyden JP. Safety and efficacy of co-trimoxazole for treatment and prevention of *Plasmodium falciparum* malaria: a systematic review. *PLoS One* 2013; **8:** e56916.

54 Klement E, Pitche P, Kendjo E, et al. Effectiveness of co-trimoxazole to prevent *Plasmodium falciparum* malaria in HIV-positive pregnant women in sub-Saharan Africa: an open-label, randomized controlled trial. *Clin Infect Dis* 2014; **58:** 651–59.

55 Manyando C, Njunju EM, Mwakazanga D, et al. Safety of daily co-trimoxazole in pregnancy in an area of changing malaria epidemiology: a phase 3b randomized controlled clinical trial. *PloS One* 2014; **9:** e96017.

56 Denoeud-Ndam L, Zannou DM, Fourcade C, et al. Cotrimoxazole prophylaxis versus mefloquine intermittent preventive treatment to prevent malaria in HIV-infected pregnant women: two randomized controlled trials. *J Acquir Immune Defic Syndr* 2014; **65:** 198–206.

57 Dow A, Kayira D, Hudgens MG, et al. The effect of cotrimoxazole prophylactic treatment on malaria, birth outcomes, and postpartum CD4 count in HIV-infected women. *Infect Dis Obstet Gynecol* 2013; **2013:** 340702.

58 WHO. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults. Geneva WHO, 2006. http://www.who.int/hiv/pub/guidelines/ctx/en/ (accessed July 7, 2014).

59 World Health Organization/UNAIDS. Provisional WHO/UNAIDS ecommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/ AIDS in Africa. *Afr Health Sci* 2001; **1:** 30–31.

60 Barker PM, Mphatswe W, Rollins N. Antiretroviral drugs in the cupboard are not enough: the impact of health systems' performance on mother-to-child transmission of HIV. *J Acquir Immune Defic Syndr* 2011; **56:** e45–48.

61 Marinda E, Humphrey JH, Iliff PJ, et al. Child mortality according to maternal and infant HIV status in Zimbabwe. *Pediatr Infect Dis J* 2007; **26:** 519–26.

62 McNally LM, Jeena PM, Gajee K, et al. Effect of age, polymicrobial disease, and maternal HIV status on treatment response and cause of severe pneumonia in South African children: a prospective descriptive study. *Lancet* 2007; **369:** 1440–51.

63 Heresi GP, Caceres E, Atkins JT, Reuben J, Doyle M. *Pneumocystis carinii* pneumonia in infants who were exposed to human immunodeficiency virus but were not infected: an exception to the AIDS surveillance case definition. *Clin Infect Dis* 1997; **25:** 739–40.

64 Sandison TG, Homsy J, Arinaitwe E, et al. Protective efficacy of co-trimoxazole prophylaxis against malaria in HIV exposed children in rural Uganda: a randomised clinical trial. *BMJ* 2011; **342:** d1617.

65 Dow A, Kayira D, Hudgens M, et al. Effects of cotrimoxazole prophylactic treatment on adverse health outcomes among HIV-exposed, uninfected infants. *Pediatr Infect Dis J* 2012; **31:** 842–47.

66 Coutsoudis A, Pillay K, Spooner E, Coovadia HM, Pembrey L, Newell ML. Routinely available cotrimoxazole prophylaxis and occurrence of respiratory and diarrhoeal morbidity in infants born to HIV-infected mothers in South Africa. *S Afr Med J* 2005; **95:** 339–45.

67 Rieder MJ, King SM, Read S. Adverse reactions to trimethoprim-sulfamethoxazole among children with human immunodeficiency virus infection. *Pediatr Infect Dis J* 1997; **16:** 1028–31.

68 Coutsoudis A, Coovadia HM, Kindra G. Time for new recommendations on cotrimoxazole prophylaxis for HIV-exposed infants in developing countries? *Bull World Health Organ* 2010; **88:** 949–50.

69 Dryden-Peterson S, Jayeoba O, Hughes MD, et al. Cotrimoxazole prophylaxis and risk of severe anemia or severe neutropenia in HAART-exposed, HIV-uninfected infants. *PLoS One* 2013; **8:** e74171.

70 Kourtis AP, Ibegbu CC, Wiener J, et al. Role of intestinal mucosal integrity in HIV transmission to infants through breast-feeding: the BAN study. *J Infect Dis* 2013; **208:** 653–61.

71 Gill CJ, Mwanakasale V, Fox MP, et al. Effect of presumptive co-trimoxazole prophylaxis on pneumococcal colonization rates, seroepidemiology and antibiotic resistance in Zambian infants: a longitudinal cohort study. *Bull World Health Organ* 2008; **86:** 929–38.

72 Mwenya DM, Charalambous BM, Phillips PP, et al. Impact of cotrimoxazole on carriage and antibiotic resistance of *Streptococcus pneumoniae* and *Haemophilus influenzae* in HIV-infected children in Zambia. *Antimicrob Agents Chemother* 2010; **54:** 3756–62.

73 Kohler PK, Chung MH, McGrath CJ, Benki-Nugent SF, Thiga JW, John-Stewart GC. Implementation of free cotrimoxazole prophylaxis improves clinic retention among antiretroviral therapy-ineligible clients in Kenya. *AIDS* 2011; **25:** 1657–61.

74 Lim PL, Zhou J, Ditangco RA, et al. Failure to prescribe pneumocystis prophylaxis is associated with increased mortality, even in the cART era: results from the Treat Asia HIV observational database. *J Int AIDS Soc* 2012; **15:** 1.

75 WHO. Global HIV/AIDS response: epidemic update and health sector progress towards universal access: WHO, UNICEF, UNAIDS. 2011. http://www.who.int/hiv/pub/progress_report2011/en/ (accessed July 7, 2014).

76 Hutchinson E, Droti B, Gibb D, et al. Translating evidence into policy in low-income countries: lessons from co-trimoxazole preventive therapy. *Bull World Health Organ* 2011; **89:** 312–16.

77 Anglaret X, Messou E, Ouassa T, et al. Pattern of bacterial diseases in a cohort of HIV-1 infected adults receiving cotrimoxazole prophylaxis in Abidjan, Cote d'Ivoire. *AIDS* 2003; **17:** 575–84.

78 Ashley EA, Lubell Y, White NJ, Turner P. Antimicrobial susceptibility of bacterial isolates from community acquired infections in Sub-Saharan Africa and Asian low and middle income countries. *Trop Med Int Health* 2011; **16:** 1167–79.

79 Chiller TM, Polyak CS, Brooks JT, et al. Daily trimethoprim-sulfamethoxazole prophylaxis rapidly induces corresponding resistance among intestinal *Escherichia coli* of HIV-infected adults in Kenya. *J Int Assoc Physicians AIDS Care (Chic)* 2009; **8:** 165–69.

80 Hamel MJ, Greene C, Chiller T, et al. Does cotrimoxazole prophylaxis for the prevention of HIV-associated opportunistic infections select for resistant pathogens in Kenyan adults? *Am J Trop Med Hyg* 2008; **79:** 320–30.

81 Madhi SA, Petersen K, Madhi A, Khoosal M, Klugman KP. Increased disease burden and antibiotic resistance of bacteria causing severe community-acquired lower respiratory tract infections in human immunodeficiency virus type 1-infected children. *Clin Infect Dis* 2000; **31:** 170–76.

82 Reddy EA, Shaw AV, Crump JA. Community-acquired bloodstream infections in Africa: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10:** 417–32.

83 Mermin J, Lule J, Ekwaru JP, et al. Cotrimoxazole prophylaxis by HIV-infected persons in Uganda reduces morbidity and mortality among HIV-uninfected family members. *AIDS* 2005; **19:** 1035–42.

84 Phetsouvanh R, Phongmany S, Soukaloun D, et al. Causes of community-acquired bacteremia and patterns of antimicrobial resistance in Vientiane, Laos. *Am J Trop Med Hyg* 2006; **75:** 978–85.

85 Cotton MF, Wasserman E, Smit J, Whitelaw A, Zar HJ. High incidence of antimicrobial resistant organisms including extended spectrum beta-lactamase producing *Enterobacteriaceae* and methicillin-resistant *Staphylococcus aureus* in nasopharyngeal and blood isolates of HIV-infected children from Cape Town, South Africa. *BMC Infect Dis* 2008; **8:** 40.

86 Scott JA, Mwarumba S, Ngetsa C, et al. Progressive increase in antimicrobial resistance among invasive isolates of Haemophilus influenzae obtained from children admitted to a hospital in Kilifi, Kenya, from 1994 to 2002. *Antimicrob Agents Chemother* 2005; **49:** 3021–24.

87 Watera C, Todd J, Muwonge R, et al. Feasibility and effectiveness of cotrimoxazole prophylaxis for HIV-1-infected adults attending an HIV/AIDS clinic in Uganda. *J Acquir Immune Defic Syndr* 2006; **42:** 373–78.

88 Everett DB, Mukaka M, Denis B, et al. Ten years of surveillance for invasive *Streptococcus pneumoniae* during the era of antiretroviral scale-up and cotrimoxazole prophylaxis in Malawi. *PLoS One* 2011; **6:** e17765.

89 Kariuki S, Revathi G, Kariuki N, Kiiru J, Mwituria J, Hart CA. Characterisation of community acquired non-typhoidal Salmonella from bacteraemia and diarrhoeal infections in children admitted to hospital in Nairobi, Kenya. *BMC Microbiol* 2006; **6:** 101.

90 van Oosterhout JJ, Laufer MK, Graham SM, et al. A community-based study of the incidence of trimethoprim-sulfamethoxazole-preventable infections in Malawian adults living with HIV. *J Acquir Immune Defic Syndr* 2005; **39:** 626–31.

91 Kamya MR, Gasasira AF, Achan J, et al. Effects of trimethoprim-sulfamethoxazole and insecticide-treated bednets on malaria among HIV-infected Ugandan children. *AIDS* 2007; **21:** 2059–66.

92 Malamba SS, Mermin J, Reingold A, et al. Effect of cotrimoxazole prophylaxis taken by human immunodeficiency virus (HIV)-infected persons on the selection of sulfadoxine-pyrimethamine-resistant malaria parasites among HIV-uninfected household members. *Am J Trop Med Hyg* 2006; **75:** 375–80.

93 Thera MA, Sehdev PS, Coulibaly D, et al. Impact of trimethoprim-sulfamethoxazole prophylaxis on falciparum malaria infection and disease. *J Infect Dis* 2005; **192:** 1823–29.

94 Musiime V, Cook A, Bakeera-Kitaka S, et al. Bacteremia, causative agents and antimicrobial susceptibility among HIV-1-infected children on antiretroviral therapy in Uganda and Zimbabwe. *Pediatr Infect Dis J* 2013; **32:** 856–62.

95 Pemba L, Charalambous S, von Gottberg A, et al. Impact of cotrimoxazole on non-susceptibility to antibiotics in *Streptococcus pneumoniae* carriage isolates among HIV-infected mineworkers in South Africa. *J Infect* 2008; **56:** 171–78.

96 Soeters HM, von Gottberg A, Cohen C, Quan V, Klugman KP. Trimethoprim-sulfamethoxazole prophylaxis and antibiotic nonsusceptibility in invasive pneumococcal disease. *Antimicrobial Agents Chemother* 2012; **56:** 1602–05.

97 Zar HJ, Hanslo D, Hussey G. The impact of HIV infection and trimethoprim-sulphamethoxazole prophylaxis on bacterial isolates from children with community-acquired pneumonia in South Africa. *J Trop Pediatr* 2003; **49:** 78–83

98 Mwansa J, Mutela K, Zulu I, Amadi B, Kelly P. Antimicrobial sensitivity in enterobacteria from AIDS patients, Zambia. *Emerg Infect Dis* 2002; **8:** 92–93.

99 Jones KDJ, Berkley JA. Severe acute malnutrition and infection; CMAM FORUM technical brief. May, 2013. http://www.cmamforum.org/resource/936 (accessed May 25, 2014).

100 Kalliomaki JL. A therapeutic trial with a combination of trimethoprim-sulphamethoxazole in rheumatoid arthritis. *Curr Ther Res Clin Exp* 1972; **14:** 22–25.

101 Valeriano-Marcet J, Spiera H. Treatment of Wegener's granulomatosis with sulfamethoxazole-trimethoprim. *Arch Intern Med* 1991; **151:** 1649–52.

102 Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CG. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. *N Engl J Med* 1996; **335:** 16–20.

103 Tadema H, Heeringa P, Kallenberg CG. Bacterial infections in Wegener's granulomatosis: mechanisms potentially involved in autoimmune pathogenesis. *Curr Opinion Rheumatol* 2011; **23:** 366–71.

104 Rozin A, Schapira D, Braun-Moscovici Y, Nahir AM. Cotrimoxazole treatment for rheumatoid arthritis. *Semin Arthritis Rheum* 2001; **31:** 133–41.

105 Ash G, Baker R, Rajapakse C, Swinson DR. Study of sulphamethoxazole in rheumatoid arthritis. *Br J Rheumatol* 1986; **25:** 285–87.

106 Ghilchik MW, Morris AS, Reeves DS. Immunosuppressive powers of the antibacterial agent trimethoprim. *Nature* 1970; **227:** 393–94.

107 Gaylarde PM, Sarkany I. Suppression of thymidine uptake of human lymphocytes by co-trimoxazole. *BMJ* 1972; **3:** 144–46.

108 Nguyen BT, Stadtsbaeder S. In vitro activity of cotrimoxazole on the intracellular multiplication of *Toxoplasma gondii*. *Pathol Eur* 1975; **10:** 307–15.

109 Nesthus I, Haneberg B, Glette J, Solberg CO. The influence of antimicrobial agents on macrophage-associated *Staphylococcus aureus*. *Acta Pathol Microbiol Immunol ScandB* 1985; **93:** 189–94.

110 Vilde JL, Dournon E, Rajagopalan P. Inhibition of *Legionella pneumophila* multiplication within human macrophages by antimicrobial agents. *Antimicrob Agents Chemother* 1986; **30:** 743–48.

111 Luppi F, Covi M, Velluti G, Spagnolo P, Fabbri LM, Richeldi L. Co-trimoxazole effect on human alveolar macrophages of AIDS patients. *J Biol Regul Homeost Agents* 2011; **25:** 461–64.

112 Anderson R, Grabow G, Oosthuizen R, Theron A, Van Rensburg AJ. Effects of sulfamethoxazole and trimethoprim on human neutrophil and lymphocyte functions in vitro: in vivo effects of co-trimoxazole. *Antimicrob Agents Chemother* 1980; **17:** 322–26.

113 Wolfish NM, Wassef N, Gonzalez H, Acharya C. Immunologic parameters of children with urinary tract infection: effects of trimethoprim-sulfamethoxazole. *Can Med Assoc J* 1975; **112:** 76–79.

114 Dubar V, Lopez I, Gosset P, Aerts C, Voisin C, Wallaert B. The penetration of co-trimoxazole into alveolar macrophages and its effect on inflammatory and immunoregulatory functions. *J Antimicrob Chemother* 1990; **26:** 791–802.

115 Ballieux BE, van der Burg SH, Hagen EC, van der Woude FJ, Melief CJ, Daha MR. Cell-mediated autoimmunity in patients with Wegener's granulomatosis (WG). *Clin Exp Immunol* 1995; **100**: 186–93.

116 Ambrose NS, Allan RN, Keighley MR, et al. Antibiotic therapy for treatment in relapse of intestinal Crohn's disease. A prospective randomized study. Dis Colon Rectum 1985; **28:** 81–85.

117 Gessler C. Favorable effect of trimethoprim-sulfonamide (Eusaprim) in a case of hemorrhagic rectocolitis. *Acta clinica Belgica* 1973; **28:** 17–19.

118 Humphrey JH. Child undernutrition, tropical enteropathy, toilets, and handwashing. *Lancet* 2009; **374:** 1032–35.

119 Prendergast AJ, Rukobo S, Chasekwa B, et al. Stunting is characterized by chronic inflammation in Zimbabwean infants. *PloS ONE* 2014; **9:** e86928.

120 Prendergast A, Walker AS, Mulenga V, Chintu C, Gibb DM. Improved growth and anemia in HIV-infected African children taking cotrimoxazole prophylaxis. *Clin Infect Dis* 2011; **52:** 953–56.

121 Prendergast AJ, Bwakura-Dangarembizi M, Musiime V, et al. Lower inflammatory biomarkers in children randomized to prolonged cotrimoxazole prophylaxis. 21st Conference on Retroviruses and Opportunistic Infections; Boston, MA, USA; March 3–6, 2014. Poster 914.

122 Tahan S, Melli LC, Mello CS, Rodrigues MS, Bezerra H, de Morais MB. Effectiveness of trimethoprim-sulfamethoxazole plus metronidazole in the treatment of small intestinal bacterial overgrowth in children living in a slum. *J Pediatr Gastroenterol Nutr* 2013; **57:** 316-18.

123 Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med* 2006; **12:** 1365–71.

124 Gough EK, Moodie EE, Prendergast AJ, et al. The impact of antibiotics on growth in children in low and middle income countries: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2014; **348:** g2267.

125 Castetbon K, Anglaret X, Attia A, et al. Effect of early chemoprophylaxis with co-trimoxazole on nutritional status evolution in HIV-1-infected adults in Abidjan, Cote d'Ivoire. *AIDS* 2001; **15:** 869–76.

126 Glennie SJ, Williams NA, Heyderman RS. Mucosal immunity in resource-limited setting: is the battle ground different? *Trends Microbiol* 2010; **18:** 487–93.

127 Prendergast A, Kelly P. Enteropathies in the developing world: neglected effects on global health. *Am J Trop Med Hyg* 2012; **86:** 756–63.

128 Alam NH, Bardhan PK, Haider R, Mahalanabis D. Trimethoprim-sulphamethoxazole in the treatment of persistent diarrhoea: a double blind placebo controlled clinical trial. *Arch Dis Child* 1995; **72:** 483–86.

129 Berkley JA, Lowe BS, Mwangi I, Williams T, Bauni E, Mwarumba S, et al. Bacteremia among children admitted to a rural hospital in Kenya. *N Engl J Med* 2005; **352:** 39–47.

130 Abrha A, Abdissa A, Beyene G, Getahun G, Girma T. Bacteraemia among severely malnourished children in Jimma University Hospital, Ethiopia. *Ethiop J Health Sci* 2011; **21:** 175–82.

131 Bachou H, Tylleskar T, Kaddu-Mulindwa DH, Tumwine JK. Bacteraemia among severely malnourished children infected and uninfected with the human immunodeficiency virus-1 in Kampala, Uganda. *BMC Infect Dis* 2006; **6:** 160.

132 Page AL, de Rekeneire N, Sayadi S, et al. Infections in children admitted with complicated severe acute malnutrition in Niger. *PLoS One* 2013; **8:** e68699.

133 Trehan I, Maleta KM, Manary MJ. Antibiotics for uncomplicated severe malnutrition. *N Engl J Med* 2013; **368:** 2436–37.

134 Smith MI, Yatsunenko T, Manary MJ, et al. Gut microbiomes of Malawian twin pairs discordant for kwashiorkor. *Science* 2013; **339:** 548–54.

135 Simoncini GM, Khanlou H. TMP/SMX is still the preferred empiric antibiotic for methicillin-resistant *Staphylococcus aureus* skin and soft tissue infection in the HIV population. *J Acquir Immune Defic Syndr* 2012; **59:** e78.

136 Chetchotisakd P, Chierakul W, Chaowagul W, et al. Trimethoprim-sulfamethoxazole versus trimethoprim-sulfamethoxazole plus doxycycline as oral eradicative treatment for melioidosis (MERTH): a multicentre, double-blind, non-inferiority, randomised controlled trial. *Lancet* 2014; **383:** 807–14.

137 Alavi SM, Alavi L. Treatment of brucellosis: a systematic review of studies in recent twenty years. *Caspian J Intern Med* 2013; **4:** 636–41.

138 Wang YL, Scipione MR, Dubrovskaya Y, Papadopoulos J. Monotherapy with fluoroquinolone or trimethoprim-sulfamethoxazole for treatment of *Stenotrophomonas maltophilia* infections. *Antimicrob Agents Chemother* 2014; **58:** 176–82.

139 Mihaila RG, Blaga L. *Burkholderia cepacia* septicemia in a patient with acute myeloid leukemia in postchemotherapy bone marrow aplasia. *Pak J Med Sci* 2013; **29:** 1275–77.

140 Angelakis E, Million M, D'Amato F, et al. Q fever and pregnancy: disease, prevention, and strain specificity. *Eur J Clin Microbiol Infect Dis* 2013; **32:** 361–68.

141 Boden K, Brueckmann A, Wagner-Wiening C, et al. Maternofetal consequences of *Coxiella burnetii* infection in pregnancy: a case series of two outbreaks. *BMC Infect Dis* 2012; **12:** 359.

142 Forgacs P, Wengenack NL, Hall L, Zimmerman SK, Silverman ML, Roberts GD. Tuberculosis and trimethoprim-sulfamethoxazole. *Antimicrob Agents Chemother* 2009; **53:** 4789–93.

143 Huang TS, Kunin CM, Yan BS, Chen YS, Lee SS, Syu W Jr. Susceptibility of Mycobacterium tuberculosis to sulfamethoxazole, trimethoprim and their combination over a 12 year period in Taiwan. *J Antimicrob Chemother* 2012; **67:** 633–37.

144 Hasse B, Walker AS, Fehr J, et al. Co-trimoxazole prophylaxis is associated with reduced risk of incident tuberculosis in participants in the Swiss HIV Cohort Study. *Antimicrob Agents Chemother* 2014; **58:** 2363–68.

145 Hoffmann CJ, Chaisson RE, Martinson NA. Cotrimoxazole prophylaxis and tuberculosis risk among people living with HIV. *PLoS ONE* 2014; **9:** e83750.

146 Alsaad N, van der Laan T, van Altena R, et al. Trimethoprim/sulfamethoxazole susceptibility of *Mycobacterium tuberculosis*. *Int J Antimicrob Agents* 2013; **42:** 472-74.

147 Sharma NK, Garg R, Baliga S, Bhat KG. Nosocomial infections and drug susceptibility patterns in methicillin sensitive and methicillin resistant *Staphylococcus aureus*. *J Clin Diagn Res* 2013; **7:** 2178–80.

148 Campbell ML, Marchaim D, Pogue JM, et al. Treatment of methicillin-resistant *Staphylococcus aureus* infections with a minimal inhibitory concentration of 2 mug/mL to vancomycin: old (trimethoprim/sulfamethoxazole) versus new (daptomycin or linezolid) agents. *Ann Pharmacother* 2012; **46:** 1587–97.

149 Forcade NA, Parchman ML, Jorgensen JH, et al. Prevalence, severity, and treatment of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) skin and soft tissue infections in 10 medical clinics in Texas: a South Texas Ambulatory Research Network (STARNet) study. *J Am Board Fam Med* 2011; **24:** 543–50.

150 Pulido Perez A, Baniandres Rodriguez O, Ceballos Rodriguez MC, Mendoza Cembranos MD, Campos Dominguez M, Suarez Fernandez R. Skin infections caused by community-acquired methicillin-resistant Staphylococcus aureus: clinical and microbiological characteristics of 11 cases. *Actas Dermosifiliogr* 2014; **105:** 150–58.

151 Bhutta ZA. Antibiotics to promote growth in children? *BMJ* 2014; **348:** g2624.