Does Trimethoprim-Sulfamethoxazole Prophylaxis for HIV Induce Bacterial Resistance to Other Antibiotic Classes?: Results of a Systematic Review

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Background. Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis has long been recommended for immunosuppressed HIV-infected adults and children born to HIV-infected women. Despite this, many resource-limited countries have not implemented this recommendation, partly because of fear of widespread antimicrobial resistance not only to TMP-SMX, but also to other antibiotics. We aimed to determine whether TMP-SMX prophylaxis in HIV-infected and/or exposed individuals increases bacterial resistance to antibiotics other than TMP-SMX.

Methods. A literature search was conducted in Medline, Global Health, Embase, Web of Science, ELDIS, and ID21.

Results. A total of 501 studies were identified, and 17 met the inclusion criteria. Only 8 studies were of high quality, of which only 2 had been specifically designed to answer this question. Studies were classified as (1) studies in which all participants were infected and/or colonized and in which rates of bacterial resistance were compared between those taking or not taking TMP-SMX and (2) studies comparing those who had a resistant infection with those who were not infected. Type 1 studies showed weak evidence that TMP-SMX protects against resistance. Type 2 studies provided more convincing evidence that TMP-SMX protects against infection.

Conclusion. There was some evidence that TMP-SMX prophylaxis protects against resistance to other antibiotics. However, more carefully designed studies are needed to answer the question conclusively.

Trimethoprim-sulfamethoxazole (TMP-SMX) has been shown to reduce HIV-related mortality among adults and children when used as prophylaxis against opportunistic infections [1–4]. Since 2000, the World Health Organization (WHO) and Joint United Nations Programme on HIV/AIDS have recommended TMP-SMX prophylaxis for immunosuppressed adults and children born to HIV-infected women [5, 6].

The successful roll-out of antiretroviral drugs has reduced the importance of TMP-SMX prophylaxis in developed countries. However, in resource-limited settings where antiretroviral therapy coverage is still incomplete and where confirmation of HIV infection in children <18 months of age is limited, TMP-SMX prophylaxis remains vital for improving HIV management outcomes.

Despite widespread recommendations and availability of convincing evidence of the effectiveness of TMP-SMX, the implementation of its use has been poor [7]. The WHO estimated that, in 2006, only 1% of the 4

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million children eligible for TMP-SMX received it [8]. In Zimbabwe in 2007, only 10.5% of children eligible for TMP-SMX received it [9].

In Africa, barriers to implementation include shortages of trained staff, stock-outs of TMP-SMX, and failure of health care systems to identify individuals eligible for TMP-SMX prophylaxis [7]. In addition, there is anxiety that it may not be cost-effective. However new evidence of the intervention's cost-effectiveness may alleviate these concerns [10, 11].

Furthermore, there has been a concern that this intervention will not work in areas where resistance to TMP-SMX is thought to be high [7]. Fortunately, there is now convincing evidence from South Africa and Zambia that it is effective even in these settings, and indeed the beneficial effects persist even as resistance to TMP-SMX increases [7, 12, 13].

Of great importance has been the fear that blanket TMP-SMX prophylaxis may lead to an increase in resistance to other drugs besides TMP-SMX among common microbial pathogens [7, 14, 15]. There is evidence that TMP-SMX prophylaxis does not increase resistance of *Plasmodium falciparum* to pyrimethamime-sulfadoxine [14, 16]. However, it remains unclear whether TMP-SMX prophylaxis increases bacterial resistance to other classes of antibiotics [7]. Biologically, when TMP-SMX causes multidrug resistance, this is thought to be a result of coselection and transference of antibiotic resistance genes between bacteria [17]. Conversely and indirectly, TMP-SMX prophylaxis may reduce development of multidrug resistance by preventing infections and, thereby, hospitalizations and exposure to other antibiotics [7].

The aim of this systematic review was to evaluate the available evidence with regard to whether TMP-SMX prophylaxis causes an increase in bacterial resistance to other classes of antibiotics. From a public health perspective, an increase in resistance would reduce the usefulness of current first-line antibiotics and result in reduced options for treating common bacterial infections in developing countries. From an individual perspective, patients receiving TMP-SMX prophylaxis may be at increased risk of treatment failure when they acquire a bacterial infection, although this has not been demonstrated in trials evaluating the effectiveness of TMP-SMX.

METHODS

Publications were eligible for review if the study outcome included a comparison of bacterial resistance to antibiotics other than TMP-SMX between HIV-infected individuals or HIV-exposed children receiving TMP-SMX prophylaxis and those who were not.

Computer searches were conducted in the following databases on the Ovid Platform: Medline 1950 through week 4 June 2009, Embase 1980 through week 27 2009, and Global Health 1910 through June 2009. Searches were also conducted in Web of Science database (accessed 7–22 July 2009), ELDIS (accessed on 6 July 2009), and ID21 (accessed on 6 July 2009). Three concepts derived from the research question were used for the literature search: TMP-SMX prophylaxis, HIV infection, and antibiotic resistance. The first part of the search was an iterative process by which the terms and synonyms that were relevant for the search were determined. The search terms used on the Ovid Platform are shown in Table 1. The search terms for Web of Science were Topic= (cotrimoxazole or co-trimoxazole or trimethoprim-sulfamethoxazole or trimethoprim-sulphamethoxazole) and Topic= (prophyla*) and Topic= (resist* or sensit* or susceptib*) and Topic= ("human immunodeficiency virus" or HIV or "acquired immunodeficiency syndrome" or AIDS), in which * represented truncation to ensure that the search was more inclusive. Web of Science was also used to find publications that had cited studies relevant to the topic. For the search platforms in ELDIS and ID21, search terms including only the drug name TMP-SMX and its synonyms were used.

Lastly, reference lists of all papers that were deemed to be eligible during pilot searches were reviewed to identify any relevant publications that may have been cited.

The title and abstract (when available) of each publication were reviewed for relevance to the topic. When it was obvious from the title and/or abstract that a publication was not relevant, it was eliminated. When it was less clear, the full paper was read to determine whether it met all the inclusion criteria.

Eligible studies were reviewed for quality using quality assessment tools that were adapted from the United Kingdom's National Institute for Health and Clinical Excellence (NICE) guidelines [18, 19]. The tools were used to make a structured assessment of whether a study was protected from bias and confounding. Of interest in this aspect was the extent to which studies took account of these confounders: (1) stage of HIV disease, (2) previous hospitalization, and (3) previous antibiotic use. Assessments were made on whether each study had internal and external validity. A standardized form was used to extract data. One person (ELS) reviewed and extracted the data, and when there were uncertainties, advice was sought from one of the co-authors.

The findings from the studies were synthesized, with more credence being placed on studies that had fared better in the quality assessment process. In theory, it would have been possible to meta-analyze the results from studies reporting methicillin-resistant *Staphylococcus aureus* (MRSA) and studies reporting pneumococcal resistance to penicillin. In practice, however, the studies that examined penicillin resistance reported differing outcomes; thus, it was not possible to combine them. It was possible to conduct separate meta-analyses for case-control, cross-sectional, and cohort studies of infection and/or colonization with MRSA.

Table 1.   Search Terms on the Ovid Platform

Concept 1: cotrimoxazole prophylaxis	Concept 2: HIV infection	Concept 3: antibiotic resistance
Cotrimoxazole adj6[b] prophyla[a]	HIV or AIDS	Resist[a]
Co-trimoxazole adj6 prophyla[a]	MeSH terms (specific for each database)	Bacteri[a] adj6 sensitiv[a] or bacteri adj6 susceptib[a]
Trimethoprim-sulfamethoxazole adj6 prophyla[a]	The above terms were combined with operator "or"	The above terms were combined with operator ''or''
Trimethoprim-sulphamethoxazole adj6 prophyla[a]		
Bactrim adj6 prophyla[a]		
Septrin adj6 prophyla[a]		
MeSH terms (specific for each database)		
All the above terms were combined with operator ''or''		

NOTE.   Results from Concept 1, Concept 2 and Concept 3 were brought together using the operator ''and''.

[a] is a truncation sign.

[b] adj6 means the two terms are within six words of each other.

RESULTS

A total of 501 studies were identified, of which 17 remained eligible for inclusion. Figure 1 shows the elimination process for the reviewed studies.

Description of Studies

Six cohort studies [16, 17, 20–23], 4 case-control studies [24–27], 6 cross-sectional studies [28–33], and 1 before-after study [34] met the eligibility criteria (Table 2). Six studies were conducted in the United States, 4 in South Africa, 2 in Italy, and 1 in each of the following countries: Kenya, Zambia, Singapore, Spain, and France.

Only 2 studies [16, 17] were designed to determine whether TMP-SMX prophylaxis increases antibiotic resistance. The remainder examined the question as subanalyses of studies which had been designed to answer a different question.

There were 2 comparison groups for bacterial resistance to antibiotics other than TMP-SMX: studies in which all participants were infected and/or colonized and in which rates of bacterial resistance were compared between those taking or not taking TMP-SMX. Most type 1 studies reported on pneumococcal resistance to penicillin. Type 2 studies compared those who had a resistant infection/colonization with those who were not infected/colonized. Most type 2 studies reported on infection and/or colonization with MRSA.

### Description of the Quality of Studies

Studies that did not control for confounders of interest (stage of HIV disease, prior hospitalization, and previous antibiotic use) were considered to be of poorer quality. Only 8 [16, 17, 20, 23, 25, 26, 29, 31] of the 17 studies were considered to have protection from bias and confounding. The rest of the studies were not necessarily poorly conducted, but they had not been designed to primarily answer the question of this review. Only 4 studies [17, 22, 30, 32] involved children: 3 involved HIV-infected children and 1 involved HIV-exposed infants [17].

Synthesis of Findings From the Studies

When looking at the study findings according to type of comparison group, 10 studies [16, 17, 21, 22, 26, 27, 30, 32–34] were considered to have type 1 comparisons, and 7 [20, 23–25, 28, 29, 31] were considered to be type 2. Of type 1 studies, 4 [16, 17, 30, 33] were colonization studies (1 MRSA and 3 pneumococcal), 4 [21, 22, 27, 32] investigated infection (1 MRSA, 2 pneumococcal, and 1 various organisms), and 2 [26, 34] investigated both colonized and infected patients. Two of the 4 colonization studies [30, 33], neither of which were considered to be good quality (1 pneumococcal and 1 MRSA), reported increased colonization with drug-resistant bacteria. One good-quality study [16] reported no change, and another good-quality study [17] reported mixed findings; among HIV-exposed infants, TMP-SMX prophylaxis increased pneumococcal resistance to clindamycin but had no effect on pneumococcal resistance to penicillin, tetracycline, erythromycin, and chloramphenicol. Of the 4 infection studies, 2 [22](1 [27] MRSA and 1 pneumococcus, neither considered to be good quality) reported no difference in rate of infection with drug-resistant pneumococcus, and 1 [21] (not considered to be good quality) reported an increase. One study [32] had too few isolates to allow meaningful interpretation of the results despite presenting the number of drug-resistant isolates in each group (TMP-SMX vs no TMP-SMX). The 2 studies (1 good quality [26]) that investigated both colonized and infected patients reported increases in infection and/or colonization with drug-resistant bacteria.

The 2 studies (both type 1) [16, 17] that had been designed specifically to answer the question of this review showed no change in pneumococcal resistance to penicillin. However, one of these studies reported resistance to clindamycin among HIV-exposed infants, as described above [17].

Of type 2 studies, 4 investigated MRSA infection [20, 23–25], 2 investigated colonization with MRSA [29, 31], and 1 reported on colonization with vancomycin-resistant
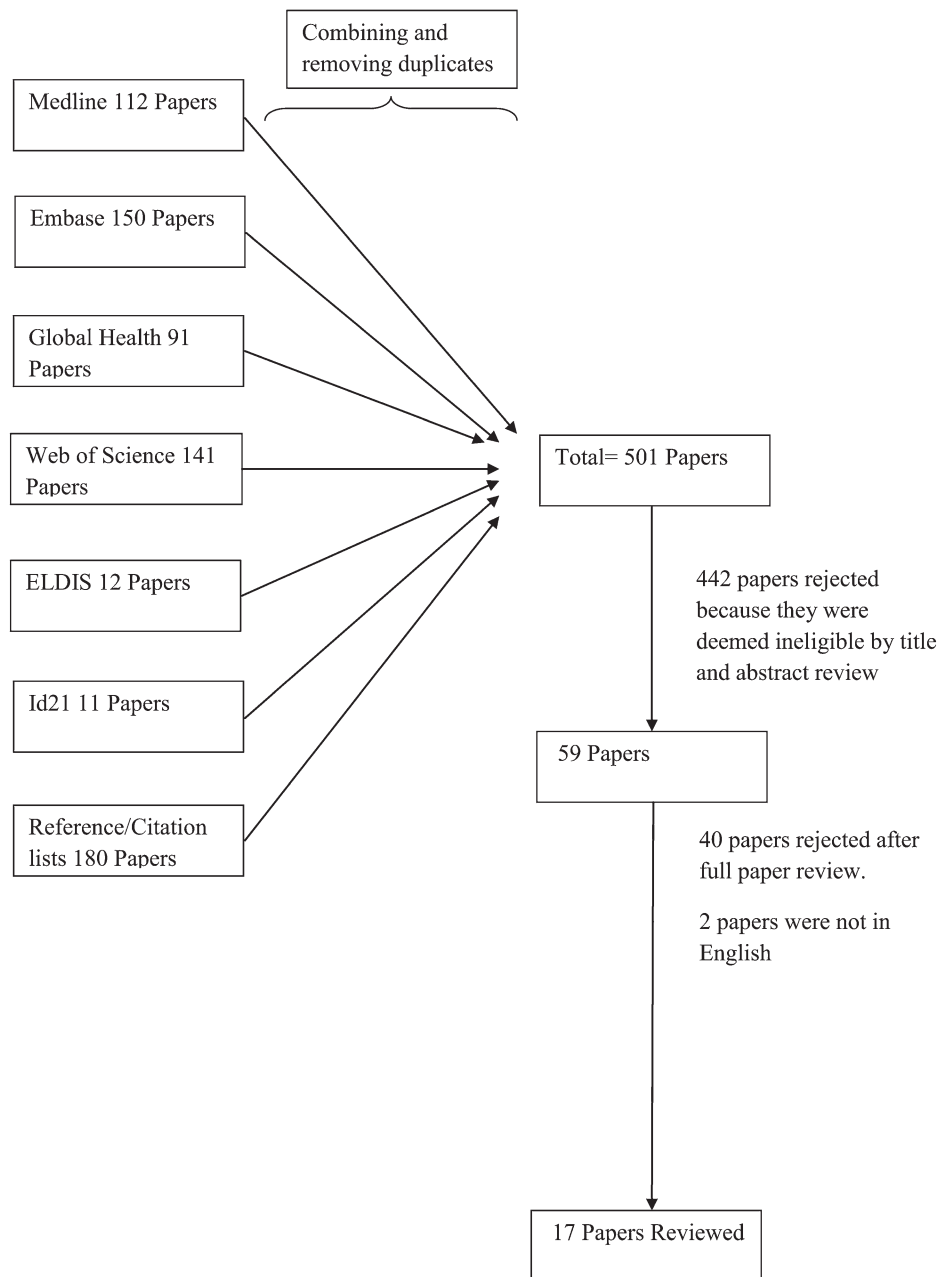
Figure 1. Process for identification of eligible publications.

enterococci [28]. Three (all considered to be good quality) [20, 23, 25] of the 4 MRSA infection studies reported a reduction in infection with MRSA, and 1 (not considered to be good quality) reported an increase in MRSA infection. The type 2 colonization studies reported no change [31] and reduced colonization [29] for 2 MRSA studies, whereas there was reported increase in colonization with vancomycin-resistant enterococcus [28].

Of the type 2 MRSA studies, there was significant heterogeneity among both the cross-sectional and case-control studies, and thus, no meta-analyses are presented. However, for cohort studies, the meta-analysis showed a protective effect of TMP-SMX prophylaxis on MRSA (relative risk, .29; 95% confidence interval, .12 - 0.7) (Figure 2); the test for heterogeneity among cohort studies was not significant ($P = .92$).

In an analysis of results according to whether the study outcome was colonization or infection, no trends were seen in the data, possibly because there were small numbers in each of the categories. In addition, no trends were noted in analysis of whether the study population comprised adults or children, because only 3 child studies were included in the synthesis, and they all had different results.

Table 2. Summary of Studies that Met the Inclusion Criteria

Author Study location Study design	Study population and size	Comparison group (Type 1 or Type 2)[c]	Reported outcomes	Results Prevalence of antibiotic resistance by group or Relative Risk/Odds Ratio (95% CI)	Study conclusions
Crum-Cianflone et al 2007 [20] USA Cohort	HIV-positive adult outpatients with controls who were not on CTX. Duration on CTX not given. N=435	Type 2	Community-acquired infection with Methicillin-Resistant *Staphylococcus Aureas* (MRSA)	CTX=0/29 (0%) CNTL=49/404 (12%) P=.06 RR not reported	CTX ↓ MRSA
Mathews et al 2005 [23] USA Cohort	HIV-positive adult patients who had been on CTX for at least 120 days. Controls had been on CTX for less than 120 days (reference in RR calculation). N=3,455	Type 2	Initial episode of clinically significant[b] MRSA infection during the study period	Prevalence not reported Unadjusted RR 0.4[a] Adjusted RR .3 (0.1–.7)[b] [a]No confidence interval given for unadjusted effect [b]Adjusted for race, HIV disease progression, and antiretroviral drug therapy	CTX ↓ MRSA infection
Jordano et al 2004 [21] Spain Cohort	HIV-positive adult patients (duration on CTX not given), with controls who were not on CTX. N=57	Type 1	Infection with pneumococcal bacterial strains with resistance to penicillin	CTX=60%[c] CNTL=38.5% P=.09 RR not reported [c]No numbers given	CTX ↑ pneumococcal resistance to penicillin
Hamel et al 2008[a] [16] Kenya Cohort	HIV-positive adults with low CD4+ cells. Exposed to CTX for six months. N=1,160	Type 1	Among patients colonized with pneumoccocus, comparison of prevalence of pneumococcal resistance to penicillin at baseline with that at 6 months after initiation of CTX prophylaxis	CTX=85% CNTL=85% RR not reported	No change in pneumococcal resistance to penicillin
Gill et al 2008[a] [17] Zambia Cohort	Infants born to HIV-positive mothers who were given CTX from six weeks of age and followed up to age 18 months (HIV-exposed infants) with HIV-unexposed infants as controls. N=260	Type 1	Among infants colonized by *S. Pneumoniae* comparison of resistance levels to each of the following drugs: clindamycin, penicillin, erythromycin, tetracycline, chloramphenicol	Prevalence not reported Unadjusted RR[d]: 1.6 (1.0–2.6)[d] 1.1 (0.7–1.7) 1.0 (0.6–1.7) 0.9 (0.6–1.5) 0.8 (0.3–2.3) [d]RR are for each of the following drugs respectively: Clindamycin, penicillin, erythromycin, tetracycline, Chloramphenicol RR remained the same after adjusting for confounders	↑ resistance to clindamycin but no change in pneumococcal resistance to penicillin, erythromycin, tetracycline, and Chloramphenicol

Table 2. (*Continued*)

Author Study location Study design	Study population and size	Comparison group (Type 1 or Type 2)[c]	Reported outcomes	Prevalence of antibiotic resistance by group or Relative Risk/Odds Ratio (95% CI)	Study conclusions
				Results	
Madhi et al 2000 [22] South Africa cohort	HIV-positive children. Controls were also HIV positive who were not on CTX for unspecified reasons. Duration on CTX not given. N=146.	Type 1	Infection with *S. Pneumoniae* resistant to penicillin, cefotaxime, TMP-SMX, tetracycline, chloramphenicol, erythromycin, clindamycin, rifampicin	Cotrimoxazole prophylaxis had no impact on resistance to other antibiotics, no other data given	CTX had no impact on pneumococcal resistance to other antibiotics
Drapeau et al 2007 [24] Italy case-control	HIV-positive patients admitted to a hospital in Italy. Duration on CTX not given. N=81	Type 2	Cases were defined as HIV-positive patients who developed clinically significant[b] MRSA infection. Controls were HIV-positive patients who did not develop MRSA	Prevalence not applicable Unadjusted OR 3.06 (.99–9.41) Adjusted OR not given	CTX ↑ MRSA
Lee *et al* 2005 [25] USA case-control	HIV-positive MSM receiving care at three participating clinics in Los Angeles County. Duration on CTX not given. N=111	Type 2	A case was the onset of a culture-positive MRSA skin infection in an HIV-positive MSM. A control was an HIV-positive MSM without skin symptoms	Prevalence not applicable Unadjusted OR .3 (0.1–.9) Adjusted OR .2 (0.1–.8)[f] [f]Adjusted for history of hospitalization, race and ethnicity, and number of sex partner	CTX ↓ MRSA
Meynard et al 1996 [26] France case-control	Hospitalised HIV-positive patients. Duration on CTX not given. N=45	Type 1	Cases were patients with *S. Pneumoniae* isolates that were intermediately or fully resistant to penicillin; and controls were patients with *S. Pneumoniae* isolates that were susceptible to penicillin	Prevalence not applicable Unadjusted OR 5.0 (1.9–13.3) Adjusted OR: 4.4 (1.6–7.0)[g] 4.9 (2.1–11.7)[h] [g]Adjusted for CD4+ count [h]Adjusted for previous hospitalization	CTX ↑ pneumococcal resistance to penicillin
Tumbarello et al 2002 [27] Italy case-control	HIV-infected patients aged >18 years with *S. aureus* bacteremia. Duration on CTX not given N=129	Type 1	Cases were HIV-positive patients with MRSA bacteremia and controls were defined as HIV-positive patients with MSSA bacteremia	Prevalence not applicable Unadjusted OR .76 (.36–1.60) Adjusted OR not given	CTX had no impact on MRSA

Table 2. (*Continued*)

Author Study location Study design	Study population and size	Comparison group (Type 1 or Type 2)[c]	Reported outcomes	Prevalence of antibiotic resistance by group or Relative Risk/Odds Ratio (95% CI)	Study conclusions
				Results	
Achenbach et al 2006 [28] USA cross-sectional	HIV-positive adults, some on CTX and some not. Duration on CTX not given. N=85	Type 2	Prevalence of colonization with vancomycin resistant enterococcus	The only data presented is that colonization with resistant bacteria was associated with TMP-SMX prophylaxis, $P=.05$	CTX ↑ resistance of enterococcus to penicillin
Cenizal et al 2008 [29] USA cross-sectional	HIV-positive adults, some on CTX and some not. Duration on CTX not given. N=146	Type 2	Prevalence of nasal colonization with MRSA	CTX=0/29 (0%) CNTL=15/102 (15%) $P=.04$	CTX ↓ MRSA
Cotton et al 2008 [30] South Africa cross-sectional	HIV-positive children, some on CTX and some not. Duration on CTX not given. N=203	Type 1	Nasal colonization with *S. Aureus*	CTX: 87% CNTL: 70% $P=.002$ RR not reported	CTX ↑ MRSA
Pemba et al 2008 [33] South Africa cross-sectional	HIV-positive mine workers, some on CTX and some not. Duration on CTX not given. N=856	Type 1	Prevalence of penicillin resistant Pneumococcus among patients who were colonized	CTX=7/23 (30%) CNTL=4/49 (8%) Unadjusted RR 4.92 (1.27–19.7) Adjusted RR not given	CTX ↑ pneumococcal resistance to penicillin
Villacian et al 2004 [31] Singapore cross-sectional	HIV-positive adults, some on CTX and some not. Duration on CTX not given. N=195	Type 2	Prevalence of colonization with MRSA	Prevalence not reported Unadjusted RR 19.4 (1.2–347.4 Adjusted RR values not given, but after adjustment for confounders TMP-SMX was not associated with MRSA	CTX had no impact on MRSA
Zar et al 2003 [32] South Africa cross-sectional	HIV-positive children, some on TMP-SMX and some not. N=151	Type 1	Five different bacterial pathogens were cultured: *K. Pneumonia; S.Aureus H. Influenza, S. Pneumonia, M.Catarrhalis*. Prevalence of resistance of each organism to 3 or 4 different drugs was determined.	Data not presented in a way that allowed interpretation for this review: Of the pneumoccocal isolates from children taking prophylaxis, two were sensitive, three were intermediately resistant and one was resistant to penicillin. The single isolate from a child not on prophylaxis was penicillin-sensitive.	

Table 2. (*Continued*)

| Author Study location Study design	Study population and size	Comparison group (Type 1 or Type 2)[c]	Reported outcomes	Results Prevalence of antibiotic resistance by group or Relative Risk/Odds Ratio (95% CI)	Study conclusions
Martin *et al* 1999 [34] USA before-after	Hospital patients. Antibiotic resistance levels were compared between the period during (n=19,514, 30,886 cultures) and one before (n not given, 24,884 cultures) widespread implementation of TMP-SMX prophylaxis.	Type 1	Resistance of *E.Coli* and *S. Aureas* species among colonized or infected HIV-positive individuals were compared between two periods	CTX=72%; CNTL=41%[l] CTX=14%, CNTL=0% [m] CTX=21%; CNTL=0% [n] CTX=16%; CNTL=4% [o] CTX=14%; CNTL=0% [p] RR not reported [l,m]Resistance of *E. Coli* to ampicillin and cephazolin respectively. [n,o,p]Resistance of *S. Aureas* to ciprofloxacin, nafcillin and gentamicin respectively. In *E. Coli* and *S. Aureas* HIV-infected patients with CTX resistance were significantly more likely to display resistance to other antibiotics.	CTX ↑ Resistance of *E. Coli* and *S. Aureus*

NOTE. CTX=Cotrimozaxole; CNTL=Control; MRSA=Methicillin Resistant *Staphylococcus Aureas*, MSSA=Methicillin Susceptible *Staphylococcus Aureas*, RR=Relative Risk, OR=Odds Ratio, MSM=Men having sex with men, CD4+=CD4+ T lymphocyte count.

[a] The study was designed to look at the effect of TMP-SMX prophylaxis on resistance levels.

[b] Clinically significant infection-Generally described in the specified papers as clinician diagnosis of infection as opposed to colonisation, and isolation of bacteria from a normally sterile body site.

[c] 1=Comparison group is based on having sensitive bacterial infection/colonisation; 2=comparison group is based on having no infection/colonisation at all.
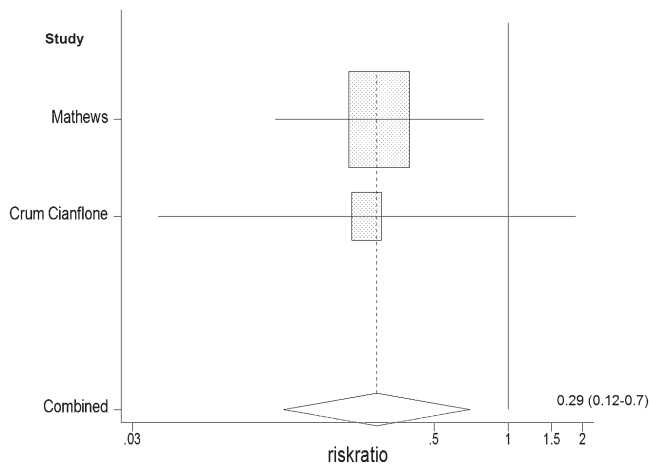
Figure 2. Meta-analysis of MRSA cohort studies.

DISCUSSION

Seventeen of 501 studies identified met the eligibility criteria of this review. Of 8 studies that were considered to have fair protection from bias and confounding, only two studies had been designed to evaluate the effect of TMP-SMX prophylaxis on antibiotic resistance. In the remainder of the studies, the effect of TMP-SMX was examined in subanalyses, which often had low precision.

The studies could be classified according to types of comparison group: type 1 were studies in which the analysis included patients who were all infected/colonized and comparisons of antibiotic resistance levels were made between those receiving TMP-SMX and those who were not; type 2 studies straightforwardly compared patients who developed a drug-resistant infection/colonization with those who had no infection/ colonization. No patterns were seen in the type 1 studies. Of 3 studies that were considered to be good quality in this group, 1 reported no change in pneumococcal resistance after TMP-SMX use, 1 reported an increase in resistance, and 1 reported mixed findings: an increase in pneumocccal resistance to clindamycin but no change in resistance to 4 other drugs.

For the type 1 studies, it may be appropriate to place additional weight on the 2 cohort studies that were specifically designed to evaluate the effect of TMP-SMX prophylaxis on antibiotic resistance [16, 17]. The rationale for this is 2-fold: first, cohort studies are the most robust designs for observational studies, because they are the least likely to have bias and confounding. Second, because the studies were designed to evaluate the effect of TMP-SMX on antibiotic resistance, they are likely to produce more reliable results than smaller subanalyses of studies designed to answer a different question.

Gill et al compared HIV-exposed infants with HIV-unexposed infants [17]. There is evidence that HIV-exposed infants are colonized and infected more than HIV-unexposed

patients [22, 35, 36]. There is also evidence that HIV-infected individuals are more likely to be colonized and infected by antibiotic-resistant bacteria [30]. In accordance with this, comparison of HIV-exposed and nonexposed children should show that HIV-exposed children have higher antibiotic resistance levels. However, the findings by Gill et al do not show this expected difference in 4 of 5 classes of antibiotics that were investigated, possibly because TMP-SMX has a protective effect, which makes HIV-exposed children similar to HIV-unexposed children [17]. Carefully designed observational studies to test this theory should be conducted in low-income countries where TMP-SMX prophylaxis is recommended for HIV-exposed children.

In contrast to type 1 studies, for type 2 studies, there was stronger evidence that TMP-SMX prophylaxis protects from infection with drug-resistant bacteria. Four studies, all considered of good quality, reported reduced infection and/or colonization with MRSA, and 1 study, also of good quality, reported no change in colonization with MRSA. The 2 lower-quality studies in this group reported increased MRSA. The meta-analysis of MRSA cohort studies revealed a 70% protective effect of TMP-SMX prophylaxis from MRSA infection (relative risk, .29; 95% confidence interval, .12–.7)

It is plausible that TMP-SMX prophylaxis protects against infection with drug-resistant bacteria. TMP-SMX may directly protect against colonization and/or infection with drug-susceptible bacterial pathogens [3], and indirect protection may arise as a result of this as the individual is less exposed to conditions that have been found to be risk factors for infection and/ or colonization with drug-resistant bacteria. For example, the patient may no longer need frequent hospitalization or will be less likely to be exposed to intravenous catheters, conditions that have been shown to increase antibiotic resistance [31]. As a result, the patient may be less likely to receive other antibiotics for treatment of infections, and such exposure to antibiotics has been shown to increase antibiotic resistance [27].

The finding by Gill et al that pneumococcal resistance to 1 of 5 antibiotics increased whereas there was no change in the resistance levels for the other 4 drugs might mean that it is possible for TMP-SMX prophylaxis to increase bacterial resistance to some classes of antibiotics but not to others [17]. This may be feasible if the mechanism of development of resistance to TMP-SMX is linked to that of the other antibiotic. Multidrug resistance can be horizontally transferred between bacterial species and genus borders if the genes that code for multidrug resistance are located on transferable plasmids or transposons [37]. It has been proposed that TMP-SMX prophylaxis may cause resistance to clindamycin or penicillin through co-selection of linked antibiotic resistance genes. [17, 26]

The strength of the Hamel et al [16] study is that it was adjusted for baseline antibiotic resistance levels. Results from that study suggest that there is no effect of 6 months of

TMP-SMX prophylaxis on antibiotic resistance among similarly exposed HIV-infected adults. This may also be explained by possible protection of TMP-SMX from infections, as explained above. Of note, the 2 studies that were designed to answer the question of this review reported no change in pneumococcal resistance to penicillin.

The meta-analysis of studies relating to colonization and/or infection with MRSA shows the potential effect of differing study designs on resistance outcomes. The 2 cohort studies (ie, the most robust studies) clearly showed reduced MRSA colonization and/or infection, both individually and when combined, whereas the cross-sectional and case-control studies showed no effect.

This literature review had several limitations. Because TMP-SMX prophylaxis has long been proven to save lives of HIV-infected patients, only observational studies, which have more potential for bias and confounding, were available for review. Most studies did not control for factors that are known to independently increase antibiotic resistance. For example, only 3 studies adjusted for HIV disease progression or previous hospitalization. Previous hospitalization has been reported as an important risk factor for colonization or infection with MRSA [24, 25, 38].

Most studies did not provide data on the duration of exposure to TMP-SMX prophylaxis. Of the studies that did, the duration of exposure is shorter than expected in clinical practice in resource-limited settings. Because of the shortage of antiretroviral therapy in such settings, HIV-infected adults are likely to be receiving TMP-SMX prophylaxis for much longer periods than was evaluated in these studies. However, the finding from Gill et al may be more generalizable to HIV-exposed infants, because TMP-SMX was given according to guidelines used in many resource-limited settings [17].

Most studies only evaluated resistance to 1 antibiotic. This makes it difficult to know whether findings can be applied across different antibiotic classes.

The other limitation of the review was the heterogeneity of study designs, class of bacteria, and drug classes investigated, which makes comparing study findings problematic and makes it inappropriate to conduct a meta-analysis for all studies.

CONCLUSIONS AND RECOMMENDATIONS

After placing weight on good-quality studies and additional weight on studies that were specifically designed to determine whether TMP-SMX prophylaxis increases antibiotic resistance, the findings of this review offer suggestive evidence that TMP-SMX prophylaxis for opportunistic infections in HIV protects against development of bacterial resistance to other classes of antibiotics. More carefully designed studies should be conducted to answer this question. It is important to ensure that future studies evaluate the importance of duration of exposure to TMP-SMX on antimicrobial resistance.

Ideally, microbial resistance surveys should be included with TMP-SMX implementation in developing countries to alert providers to any changes in drug resistance patterns.

Of most importance, the fear of antibiotic resistance should not stop health care providers from giving TMP-SMX to individuals who need it.

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