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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	3
OBJECTIVES	3
METHODS	3
RESULTS	4
DISCUSSION	5
AUTHORS' CONCLUSIONS	5
ACKNOWLEDGEMENTS	5
REFERENCES	6
CHARACTERISTICS OF STUDIES	6
DATA AND ANALYSES	7
Analysis 1.1. Comparison 1 Cotrimoxazole versus control, Outcome 1 Death.	7
Analysis 1.2. Comparison 1 Cotrimoxazole versus control, Outcome 2 Adverse events.	8
Analysis 1.3. Comparison 1 Cotrimoxazole versus control, Outcome 3 Hospital admission.	8
Analysis 1.4. Comparison 1 Cotrimoxazole versus control, Outcome 4 Death by age.	8
Analysis 1.5. Comparison 1 Cotrimoxazole versus control, Outcome 5 Death by CD4%.	9
WHAT'S NEW	9
HISTORY	9
CONTRIBUTIONS OF AUTHORS	10
DECLARATIONS OF INTEREST	10
SOURCES OF SUPPORT	10
INDEX TERMS	10

[Intervention Review]

Cotrimoxazole prophylaxis for opportunistic infections in children with HIV infection

Kate Grimwade¹, George H Swingler²¹Birmingham, UK. ²School of Child and Adolescent Health, University of Cape Town, ICH Building, Red Cross Children's Hospital, Cape Town, South Africa**Contact address:** Kate Grimwade, 8 Westgate Apartments, 10 Arthur Place, Birmingham, B1 3DB, UK. kategrimwade@mac.com.**Editorial group:** Cochrane HIV/AIDS Group**Publication status and date:** Edited (no change to conclusions), published in Issue 1, 2009.**Citation:** Grimwade K, Swingler GH. Cotrimoxazole prophylaxis for opportunistic infections in children with HIV infection. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD003508. DOI: [10.1002/14651858.CD003508.pub2](https://doi.org/10.1002/14651858.CD003508.pub2).

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ABSTRACT

Background

The majority of children with HIV infection live in low-income countries without access to antiretroviral drugs. The prevention and early treatment of opportunistic infections are the mainstay of their medical management. Cotrimoxazole is cheap and effective against a wide range of organisms, including *Pneumocystis jiroveci* pneumonia (PCP), which is an important cause of death and illness in the first year of life. It is safe with relatively few side effects. Diagnosis of HIV in children is complicated by the presence of maternal antibodies in early life. Providing prophylaxis based initially on maternal status is one possible solution. However, routine prophylactic treatment is difficult to deliver in low-resource settings, and could also lead to increased resistance to the drug.

Objectives

To assess the effects of routinely administered cotrimoxazole on death and illness episodes in children with HIV infection, and in infants of HIV-infected mothers.

Search methods

We searched the Cochrane HIV/AIDS registry, MEDLINE, the Cochrane Controlled Trials Register, LILACS, AIDSLINE, AIDSTRIALS and AIDSDRUGS databases, and proceedings and abstracts from AIDS and TB conferences (search date Feb 2005). We checked reference lists of pertinent articles, and contacted pharmaceutical companies and experts in the field.

Selection criteria

Randomised or quasi-randomised trials comparing routinely administered cotrimoxazole versus placebo or no treatment in children (age less than 15 years) with HIV infection, or children less than 18 months with HIV infected mothers.

Data collection and analysis

Two reviewers independently assessed trial eligibility and quality. Where data were incomplete or unclear trial authors were contacted for further details.

Main results

One study was identified that fulfilled the inclusion criteria. It studied 534 children with HIV infection in Lusaka, Zambia. The study was conducted in an area of high bacterial resistance to cotrimoxazole (60-80%). A reduction in mortality of 33% was seen in the cotrimoxazole group as compared to placebo, relative risk 0.67 (95% CI 0.53 - 0.85). There was also a beneficial effect on hospitalisation, relative risk 0.77 (95% CI 0.62 - 0.96). There was no difference in adverse events between groups, and the beneficial effect was seen across all ages and CD4%.

Authors' conclusions

A single trial has shown a beneficial effect from the use of cotrimoxazole prophylaxis in HIV infected children in Zambia. It must be decided whether this can be extrapolated to other resource-poor settings.

PLAIN LANGUAGE SUMMARY

The majority of children with HIV infection live in low-income countries without access to antiretroviral drugs. The prevention and early treatment of opportunistic infections are the mainstay of their medical management. Cotrimoxazole is cheap and effective against a wide range of organisms, including *Pneumocystis jiroveci* pneumonia (PCP), which is an important cause of death and illness in the first year of life. It is safe with relatively few side effects.

One study fulfilled the inclusion criteria for this review. This was a well-conducted trial of good methodological quality. It shows a significant reduction in mortality in children between the ages of 1 and 15 years, taking cotrimoxazole in comparison to placebo. Using cotrimoxazole in HIV-infected children waiting for antiretroviral treatment, or not yet requiring it, may increase survival and reduce the number of days spent in hospital.

BACKGROUND

Human immunodeficiency virus (HIV) damages the immune system of people it infects, making secondary (or opportunistic) infections more common. Since the start of the HIV epidemic, the importance of opportunistic infections in the course of the disease and the potential for preventing them by antibiotic prophylaxis has been recognised. Prophylaxis has been widely used (Fischl 1988). Antibiotic prophylaxis in these circumstances is an alternative to prompt treatment, and the aim is to reduce the occurrence of the opportunistic illnesses, hence delaying death.

In some settings, people with HIV infection are heavily exposed to common pathogens that cause moderate to severe illness, whatever the person's immunity may be. This is particularly true for people living in poverty in developing countries, in whom common pathogens cause high levels of illness and can contribute to early mortality. In these groups, prophylaxis with broad-spectrum antibiotics has been considered as a means to improve the quality and duration of life.

The spectrum of opportunistic pathogens varies across the world. In the developed world, previously rare infections such as *Pneumocystis carinii* pneumonia (PCP), now known as *P. jiroveci*, have emerged in the context of AIDS (Gottlieb 1981). In the developing world, where most of the HIV/AIDS burden is borne (UNAIDS 2000), children are heavily exposed to common pathogens, and those with HIV infection are at increased risk of bacterial infections such as diarrhoeal disease and pneumonia. Common bacterial pathogens include *Pneumococcus*, *Staphylococcus*, *non-typhi Salmonellae* and other gram-negative organisms. *Haemophilus influenzae* remains an important pathogen in children under five years because immunization against *Haemophilus*, routinely practised in industrialised countries, is still prohibitively expensive for many developing countries. PCP is an important cause of death in those under the age of 12 months, but is seen infrequently after that age (Ikeogu 1997, Zar 2000).

Cotrimoxazole prophylaxis for both adults and children with HIV infection has been recommended internationally (WHO/UNAIDS 2000) following the promising findings of two studies in West Africa, in adult populations (Anglaret 1999, Wiktor 1999). (The effect of cotrimoxazole in adults is addressed in a separate review [Grimwade 2002].)

HIV-infected children differ from adults in a number of ways. *Haemophilus influenzae* remains an important pathogen in children in developing countries and PCP is a much more important infection in infants than in adults in low-income countries. The progression of disease in young children is also more rapid than in adults. About a quarter of infected children die in the first year (Peckham 1995). Explanations for this include an immature immune system at the time of HIV acquisition, the different infecting dose and route of infection, and to primary infections with opportunistic organisms, rather than reinfection or reactivation of infections (Peckham 1995).

An additional consideration in children is that the diagnosis of HIV infection is difficult (or very expensive) in the first eighteen months of life, because of the presence of maternal HIV antibodies in the child's blood. Because PCP is an important cause of death in those under the age of 12 months (Ikeogu 1997, Zar 2000) and may be

the first manifestation of the illness, prophylaxis has been given to exposed children before it is known whether they are HIV-infected. As increasing numbers of HIV-infected pregnant women are being identified in programmes to prevent mother to child transmission of HIV, this practice is becoming more common.

Adverse effects of cotrimoxazole given routinely range from skin rashes and gastrointestinal upsets to life threatening blood disturbances. The routine use of cotrimoxazole could also hasten the development of bacterial resistance, rendering it useless when required to treat infection. Any beneficial effects thus need to be weighed against harms and other costs. Delivery of chemoprophylaxis in low-income settings is expensive and logistically difficult. The size of the effect of chemoprophylaxis is thus important in assessing its cost-effectiveness compared with other healthcare interventions.

OBJECTIVES

To assess the effects of routinely administered cotrimoxazole on death and illness episodes in HIV infected children or infants of HIV-infected mothers.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials

Types of participants

Children aged less than 15 years who are infected with HIV, or less than 18 months with HIV-infected mothers.

Types of interventions

Intervention: Cotrimoxazole, given routinely.
Control: Placebo or no treatment.

Types of outcome measures

Primary Outcome

Mortality, expressed as number of deaths occurring during the follow up period

Secondary outcomes:

- Serious morbid events as defined by the trial researchers
- Admissions to hospital
- Adverse events, defined as those causing cessation of the therapy or hospitalisation
- Type of infection:
 - PCP
 - Toxoplasmosis
 - Bacterial infections
 - Parasitic infections, excluding toxoplasmosis
 - Fungal infections, excluding PCP

Studies failing to meet these criteria were excluded from the review.

Search methods for identification of studies

A search for studies was performed using the Cochrane HIV/AIDS registry, MEDLINE, EMBASE, CENTRAL/CCTR, AIDSLINE, AIDSTRIALS and AIDSDRUGS databases. Proceedings and abstracts from the

international AIDS conferences were searched and experts were contacted in an attempt to identify unpublished research or trials still underway. Reference lists from reports of pertinent articles were searched. Pharmaceutical companies (Glaxo-SmithKline and Roche) were approached for any unpublished data on this topic. Studies in all languages were considered.

Data collection and analysis

Eligibility

Study eligibility was judged independently by two reviewers, who reviewed the abstracts identified in the above searches. If the title of a report was judged potentially to be relevant by either reviewer, the abstract was reviewed by both. If the abstract was judged by either reviewer to be potentially eligible, the full article was then examined. Disagreements were resolved by discussion.

Data collection

Characteristics of included studies and data were extracted independently by two reviewers using a standard form. Data retrieved from the reports included study design and methodological quality, participant characteristics (age, concomitant TB, stage of disease), trial setting (including level of resistance to cotrimoxazole), interventions, co-interventions (including antiretroviral use) and outcomes.

The quality of included trials was assessed independently by two reviewers according to the following criteria.

1. Allocation Concealment

- Adequate measures to conceal allocations, such as central randomisation; serially numbered, opaque sealed envelopes; or other descriptions that contain convincing elements of concealment
- Unclearly concealed trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the categories above
- Inadequately concealed trials in which method of allocation is not concealed, such as alternation methods or use of case record numbers

2. Inclusion of all randomised participants

- Trials where an intention to treat analysis was possible and there were few losses to follow-up
- Trials which reported exclusions after randomisation, but exclusions were less than 10%
- No reporting on exclusions, exclusions greater than 10%, or wide differences in exclusions between groups

Analysis

A quantitative analysis was performed using the intention to treat principle. Meta-analysis was not performed as only one study was identified that fulfilled the inclusion criteria.

Occurrence of the specified outcomes was compared between participants that received prophylactic antibiotics and those that did not. Relative risks (RR) with 95% confidence intervals (CI) were calculated.

Subgroup analyses

As part of the primary analysis, subgroup analysis were conducted for:

- Bacteriological resistance of the major pathogens to cotrimoxazole in the area studied (greater than 30% - high vs. less than 30% - low)
- Comorbidity with TB (TB vs. no TB)
- Concomitant antiretroviral use (yes or no)
- CD4 ratios (<15%, >15%) (MMWR 1998).
- Age (<2yrs, >2yrs)

RESULTS

Description of studies

One study was identified that fulfilled the inclusion criteria. Chintu et al (Chintu 2004) conducted a randomised placebo controlled trial of cotrimoxazole in children in Lusaka, Zambia. They enrolled 541 children with HIV, 269 of which were randomised to receive cotrimoxazole daily, in a dose that varied according to their age: children younger than 5 years received 240mg daily (5ml suspension); those older than 5 years received 480mg daily (10ml). The control group received a matching placebo. One hundred and twenty-six (48%) of the cotrimoxazole group and 140 (52%) of the control group were male. The original study design enrolled children from the ages of 6 months to 5 years. However, with time it became apparent that children older than 5 years were being diagnosed in the study setting, and therefore the upper age limit was extended to include children up to their 15th birthday. This change in the trial results in less than 1% of patients being a maximum of 2 years above the cut-off age for this review. It was decided that it was more meaningful to keep all the patients in this review. Four months into the study, following the release on UNAIDS recommendations on the use of cotrimoxazole for children with HIV, and in recognition that PCP occurs in infants aged 6 to 12 months, there was a further amendment to enrol only children over 12 months. Thus, there were a few patients enrolled at the outset who later were not included in the study.

The children were diagnosed with HIV using antibody testing. Therefore, there were a number of infants that initially tested positive for HIV infection, but at a later date, once maternal antibodies were no longer present, were actually found to be HIV negative. These children were removed from the analysis. As a result, the final analysis was performed in 534 children, 265 who had received cotrimoxazole and 269 who had received placebo. The final study population were distributed across age groups, with 32% aged between 1-2 years, 28% between 2-5 years, 21% between 6-9 years and 15% older than 10 years. The age distribution was similar in control and intervention groups. Three quarters (75%) of all participants had been in hospital at least once, and most were symptomatic of their HIV, due to difficulties experienced in recruiting asymptomatic children from primary health care clinics. Participants in both groups had a mean CD4% of 11% and were well distributed across the range of CD4% from 0 to greater than 20%. Distribution was similar in both groups. Median follow-up was 18.9 months, with 19.4 months in the cotrimoxazole group and 17.7 months in the control group. A small number of children received antiretroviral treatment at some stage during the trial --14 (5%) children on cotrimoxazole and 11 (4%) children on placebo -- with coformulated lamivudine, stavudine and nevirapine (Triomune®) being the most commonly used combination.

The primary outcomes measured were mortality and adverse reactions. Secondary outcomes included admissions to hospital and types of infection. Resistance to cotrimoxazole amongst common bacterial pathogens in the area is stated to be between 60 and 80%.

Risk of bias in included studies

The included study (Chintu 2004) was of high methodological quality. Participants were randomly assigned to the intervention or control arm using a prepared blocked randomisation list. Codes linking allocation to study number were held at the UK Medical Research Council Clinical Trials Unit in London. Subjects and investigators were blinded to allocation. The investigators state that an intention to treat analysis was performed; however, there were a small number of exclusions after enrolment due to the amendments made to age of enrolment and misdiagnosis of 7 children with HIV, as discussed in the previous section.

Effects of interventions

The one study identified that fulfilled the inclusion criteria for this review (Chintu 2004) randomised 534 children to cotrimoxazole or matching placebo. It showed a significant beneficial effect from cotrimoxazole on mortality with the number of deaths reduced from 112 (42%) in the control group to 74 (28%) in the cotrimoxazole group. This 33% reduction represents a relative risk of 0.67 (95% CI 0.53 - 0.85). The number needed to treat to prevent one death was 7. There was no significant difference between groups in the occurrence of adverse events with 16 (6%) in the cotrimoxazole group and 18 (7%) in the control group experiencing grade 3 or 4 reactions leading to stopping of the trial drug, relative risk 0.90 (95% CI 0.47 - 1.73). The beneficial effect of cotrimoxazole was seen across all age groups. There was also benefit across the range CD4% although this failed to reach significance in the >15% group which contained small numbers.

DISCUSSION

Only one trial was identified that fulfilled the criteria for inclusion (Chintu 2004). This was a well-conducted trial of good methodological quality. It shows a significant reduction in mortality in children between the ages of 1 and 15 years, taking cotrimoxazole in comparison to placebo. There were few adverse events and the drug was well tolerated. No differences in effect were seen across age groups and CD4%. This failed to reach significance in some groups due to small sample size.

Thus far, this is the only high quality evidence for the effect of cotrimoxazole prophylaxis in children. Bearing in mind the

ongoing discussion in adult medicine on the effect of cotrimoxazole prophylaxis in that age group in the resource-poor setting, and the disagreement on the applicability of randomised controlled trials performed within one country to all low-income countries, it is yet to be seen whether this single study will be considered sufficient evidence upon which to base paediatric public health policy across the world. Given that it showed significant beneficial effect despite being conducted in the presence of high levels of bacterial resistance to cotrimoxazole, it is suggestive that this benefit may be extrapolated to other settings of similar or lower resistance. However, as it is still not possible to say what the mechanism of action of the cotrimoxazole actually is, this can only be a suggestion. There will need to be discussion as to whether further studies are required, to conclude the beneficial effect of cotrimoxazole, or whether this study is sufficient. If further placebo-controlled trials are felt to be unethical (which, as seen with adult studies, is likely) observational work looking at causes of morbidity amongst those taking cotrimoxazole and those choosing not to is needed to establish the mechanism of action of prophylaxis.

AUTHORS' CONCLUSIONS

Implications for practice

Antiretroviral treatment is becoming available in low-income countries but will take time to roll out and there will never be enough drugs for all those infected with HIV. Using cotrimoxazole in HIV-infected children waiting for antiretroviral treatment, or not yet requiring it, may increase survival and reduce the number of days spent in hospital.

Implications for research

Surveillance to evaluate the effects of widespread cotrimoxazole use on bacterial and malarial resistance will be essential to guide future treatment protocols. If it is felt that the findings of this single study cannot be automatically extrapolated to other areas, further work to look at the effect of prophylaxis will be required. It is unlikely following this trial that the use of placebo to investigate the effects of prophylaxis in children would be considered ethical.

As the provision of antiretroviral drugs for the definitive treatment of HIV infection is rolled out across low-income settings, research is needed to identify the appropriate use of cotrimoxazole in this setting, in particular looking at the safety of stopping prophylaxis once immunity has been restored on antiretroviral treatment.

ACKNOWLEDGEMENTS

Elizabeth Pienaar helped develop the search strategy and performed the electronic search.

REFERENCES

References to studies included in this review

Chintu 2004 {published data only}

Chintu C, Bhat GJ, Walker AS, Mulenga V, Sinyinza F, Lishimpi K, Farrelly L, Kaganson N, Zumla A, Gillespie SH, Nunn AJ, Gibb D. Cotrimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. *Lancet* 2004, (364):1865-71.

Additional references

Anglaret 1999

Anglaret X, Chêne G, Attia A, Toure S, Lafont S, Combe P, Manlan K, N'Dri-Yoman T, Salamon R. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1 infected adults in Abidjan, Cote d'Ivoire: a randomised trial. *Lancet* 1999, (353):1463-68.

Fischl 1988

Fischl MA, Dickinson GM, La Voie L. Safety and Efficacy of sulfamethoxazole and trimethoprim chemoprophylaxis for *Pneumocystis carinii* pneumonia in AIDS. *JAMA* 1988;**259**(8):1185-9.

Gottlieb 1981

Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, Saxon A. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired immunodeficiency. *NEJM* 1981;**305**(24):1425-31.

Grimwade 2002

Grimwade K, Swingle G. Cotrimoxazole Prophylaxis of Opportunistic Infections in Adults with HIV Infection. *Cochrane Library* awaiting publication.

Ikeogu 1997

Ikeogu MO, Wolf B, Mathe S. Pulmonary manifestations in HIV seropositivity and malnutrition in Zimbabwe. *Arch Dis Child* 1997;**76**(2):124-8.

MMWR 1998

Centers for disease control. Guidelines for the use of antiretroviral agents in pediatric HIV infection. *MMWR* 1998;**47**:1-31.

Peckham 1995

Peckham C, Gibb D. Mother-to-child transmission of the human immunodeficiency virus.. *N.Engl.J.Med* 1995;**5**(333):298-302.

Spira 1999

Spira R, Lepage P, Msellati P, Van de Perre P, Leroy V, Simonon A, Karita E, Dabis F. Natural history of human immunodeficiency virus type 1 infection in children: a five year prospective study in Rwanda. *Pediatrics*. 1999;**104**(5):e56.

Taha 2000

Taha TE, Graham SM, Kumwenda NI, Broadhead RL, Hoover DR, Markakis D, Van der Hoven L, Liomba GN, Chipangwi JD, Miotti PG. Morbidity among HIV-1 infected and uninfected African children. *Pediatrics* 2000;**106**(6):e77.

UNAIDS 2000

UNAIDS. Report on the global HIV/AIDS epidemic. June 2000.

WHO/UNAIDS 2000

WHO/UNAIDS. Provisional WHO/UNAIDS secretariat recommendations on the use of cotrimoxazole in adults and children living with HIV/AIDS in Africa. UNAIDS Geneva 2000.

Wiktor 1999

Wiktor SZ, Sassan-Morokro M, Grant AD, Abouya L, Karon JM, Maurice C, Djomand G, Ackah A, Domoua K, Kadio A, Yapi A, Combe P, Tossou O, Roels TH, Lackritz EM, Coulibaly D, De Cock KM, Coulibaly IM, Greenberg AE. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-infected patients with TB in Abidjan, Cote d'Ivoire: a randomised controlled trial. *Lancet* 1999, (353):1469-75.

Zar 2000

Zar HJ, Dechaboon A, Hanslo D, Apolles P, Magnus KG, Hussey G. *Pneumocystis carinii* pneumonia in South African children infected with human immunodeficiency virus. *Ped Inf Dis J* 2000;**19**(7):603-7.

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Chintu 2004

Methods	Prepared blocked randomisation list using masked drug labelled with sequential study numbers. Randomisation codes linking allocation to study numbers kept at MRC CTU in London. Intention to treat analysis although few exclusions (less than 10%) due to changes made to inclusion ages and misdiagnosis of HIV in 7 infants due to the presence of maternal antibodies.
Participants	541 children originally enrolled, 534 analysed between the ages of 12 months and 15 years. 265 on cotrimoxazole, 269 on placebo. Age distribution and CD4% similar across both groups. Median age 4.2 years in cotrim group, 4.5 in placebo group. Median CD4% 11% in cotrim group 10% in placebo group.

Cotrimoxazole prophylaxis for opportunistic infections in children with HIV infection (Review)

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Chintu 2004 (Continued)

48% male in cotrim group, 52% in placebo group. 14 children (5%) on cotrim and 11 (4%) on placebo received antiretroviral treatment at some time during the study.

Interventions	Cotrimoxazole group given 240mg (5ml suspension) if under 5 years, 480mg (10ml) if over 5 years. Control group received matching placebo.
Outcomes	Primary outcome - mortality, adverse reactions. Secondary outcomes not clearly stated but hospital admissions and some causes of morbidity reported on.
Notes	Bacterial resistance to cotrimoxazole in the most common pathogens in the area reported to be between 60 and 80%

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

DATA AND ANALYSES

Comparison 1. Cotrimoxazole versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	534	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.53, 0.85]
2 Adverse events	1	534	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.47, 1.73]
3 Hospital admission	1	534	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.62, 0.96]
4 Death by age	1	534	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.52, 0.84]
4.1 age <2	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.45, 0.88]
4.2 age >2	1	344	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.50, 0.97]
5 Death by CD4%	1	393	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.46, 0.84]
5.1 <15%	1	272	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.44, 0.85]
5.2 >15%	1	121	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.30, 1.47]

Analysis 1.1. Comparison 1 Cotrimoxazole versus control, Outcome 1 Death.

Study or subgroup	Cotrimoxazole n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Chintu 2004	74/265	112/269		100%	0.67[0.53,0.85]
			Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

Analysis 1.2. Comparison 1 Cotrimoxazole versus control, Outcome 2 Adverse events.

Analysis 1.3. Comparison 1 Cotrimoxazole versus control, Outcome 3 Hospital admission.

Analysis 1.4. Comparison 1 Cotrimoxazole versus control, Outcome 4 Death by age.

Analysis 1.5. Comparison 1 Cotrimoxazole versus control, Outcome 5 Death by CD4%.

WHAT'S NEW

Date	Event	Description
29 October 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2002

Review first published: Issue 2, 2003

Date	Event	Description
26 September 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Both reviewers participated in protocol development, the literature search and in writing the final report.

DECLARATIONS OF INTEREST

KCG is supported by DFID (Department for International Development) to investigate the effectiveness of cotrimoxazole prophylaxis when implemented in a rural resource poor setting. DFID is the British government aid and development agency.

GS: None declared.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department for International Development, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

AIDS-Related Opportunistic Infections [*prevention & control]; Anti-Infective Agents [*therapeutic use]; Randomized Controlled Trials as Topic; Trimethoprim, Sulfamethoxazole Drug Combination [*therapeutic use]

MeSH check words

Child; Humans; Infant