

Prophylactic antibiotics to prevent pneumonia and other complications after measles: community based randomised double blind placebo controlled trial in Guinea-Bissau

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Abstract

Objective To investigate whether prophylactic antibiotics can prevent complications of measles.

Design Community based, randomised, double blind, placebo controlled trial.

Setting Bandim Health Project study area in Bissau, Guinea-Bissau, west Africa.

Participants 84 patients with measles during a measles epidemic in Bissau in 1998 (fewer than originally planned owing to interruption by war).

Interventions Sulfamethoxazole-trimethoprim (co-trimoxazole) or placebo for seven days.

Main outcome measures Pneumonia and admission to hospital. Also weight change during the first month of infection, diarrhoea, severe fever, oral thrush, stomatitis, conjunctivitis, and otitis media.

Results The median age of the patients with measles was 5.4 (range 0.49-24.8) years. One of 46 participants who received co-trimoxazole developed pneumonia, in contrast to six of 38 participants who received placebo (odds ratio 0.08 (95% confidence interval 0 to 0.56), adjusted for age group). The number needed to treat was 7 (4 to 48). All three participants admitted to hospital had received placebo ($P=0.09$). The weight gain during the first month after inclusion was 15 (2-29) g/day in the placebo group and 32 (23-42) g/day in the co-trimoxazole group ($P=0.04$, adjusted for age group, weight for age at inclusion, measles vaccination status, and duration of disease).

Significantly less conjunctivitis occurred among recipients of co-trimoxazole than placebo, as well as a non-significant tendency to less diarrhoea, severe fever, oral thrush, and stomatitis. Complications of otitis media were the same in the two groups.

Conclusions The group that received prophylactic antibiotics had less pneumonia and conjunctivitis and had significantly higher weight gains in the month after inclusion. The results indicate that prophylactic antibiotics may have an important role in the management of measles infection in low income countries.

Trial registration Clinical trials NCT00168532.

Introduction

The case fatality rate of measles in developing countries is high, reaching 30% among patients admitted to hospital.¹ Even in affluent countries, the complication rate is high and epidemics cause severe morbidity, permanent sequelae, and death.² Trials of prophylactic antibiotics in measles infection were made several years ago, but none complied with the current standards for design of a randomised controlled trial.³ In 1987 a project in Senegal implemented routine prophylactic antibiotics for children under 3

years of age.⁴ The study found a twofold reduction in the case fatality rate for measles in the cohort that received prophylactic antibiotics compared with historical controls. The World Health Organization proposed that a priority for measles research should be a randomised, double blind, placebo controlled trial of prophylactic antibiotics in measles.⁵ Here we report results from a trial done in Guinea-Bissau in 1998.

Methods

The study took place in 1998 in Bissau, Guinea-Bissau, west Africa, under the Bandim Health Project.⁶ The project's surveillance system registers deaths, infections, and vaccinations. Coverage of measles vaccine was 89%.⁷

We detected patients with measles and suspected measles through the surveillance system, morbidity surveillance of the youngest children, consultations at the two health centres, and hospital admissions at the paediatric department in Bissau. Project physicians diagnosed measles and referred patients with measles for chest radiography on suspicion of pneumonia (see bmj.com).

We started the study in January 1998. The inclusion criteria were a clinical diagnosis of probable measles in the prodromal phase or within the first seven days after the onset of rash. Patients were randomly assigned either co-trimoxazole or placebo. Both patients and researchers were blinded to allocation. The duration of treatment was 7 days. A physician visited participants twice a week during the first two weeks and once a week during weeks three and four. If signs of bacterial pneumonia developed, chest radiography was done. The result of chest radiography determined further case management (see bmj.com).

We took two blood specimens four to six weeks apart for measurement of measles antibodies. We considered a fourfold increase or decrease in IgG antibody concentration or a positive IgM test to be serological confirmation.

Analytical methods

The main outcome measure was treatment failure due to pneumonia, admission to hospital, or both. Other outcome measures were weight change during the first month of infection, diarrhoea, severe fever, oral thrush, stomatitis, conjunctivitis, and otitis media. We adjusted main analyses for age group, vaccination status, weight for age, and duration of disease. We based the main analyses on intention to treat. We defined a death from measles as a death occurring within 30 days after the rash.

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Table 1 Intention to treat analyses of outcome measures. Values are numbers (percentages) unless stated otherwise

	Co-trimoxazole (n=46)	Placebo (n=38)	Odds ratio† (95% CI)	Adjusted odds ratio‡ (95% CI)	Adjusted odds ratio‡ (95% CI): laboratory confirmed cases
Main outcome measures					
Pneumonia after inclusion	1 (2)	6 (16)	0.08 (0 to 0.56)§	0.14 (0.01 to 1.50)§	0.11 (0 to 1.22)§
Admitted to hospital with measles after inclusion	0 (0)	3 (8)	0 (0 to 1.03)	–	–
Other outcome measures					
Diarrhoea after inclusion	3 (7)	5 (13)	0.27 (0.04 to 1.39)§	0.17 (0.01 to 1.55)§	0.10 (0 to 1.04)§
Severe fever after inclusion	6 (13)	11 (29)	0.32 (0.10 to 1.07)	0.36 (0.09 to 1.43)	0.34 (0.08 to 1.53)
Oral thrush after inclusion	0 (0)	3 (8)	0 (0 to 1.03)	–	–
Stomatitis after inclusion	4 (9)	7 (18)	0.37 (0.09 to 1.50)	0.43 (0.08 to 2.26)	0.35 (0.06 to 2.12)
Conjunctivitis after inclusion	12 (26)	17 (45)	0.36 (0.14 to 0.96)*	0.31 (0.10 to 1.03)	0.25 (0.06 to 0.96)*
Otitis media after inclusion	1 (2)	2 (5)	0.38 (0.02 to 4.42)§	0.72 (0.05 to 10.6)§	0.44 (0.01 to 6.93)§

*P<0.05.

†Controlled for age group.

‡Adjusted for age group, weight for age z score at inclusion, time since rash, and measles vaccination status.

§Profile-likelihood confidence interval.

We calculated absolute risk reduction by subtracting the pneumonia rate in the co-trimoxazole group from the pneumonia rate in placebo group. We used EPI-Info Nutrition to calculate weight for age z scores. After exclusions we included 75 participants, and we analysed weight change in a mixed linear model.

Results

Among 234 patients with measles evaluated for study entry, 84 entered the study.

Study population

Median age at inclusion was 5.4 (range 0.49-24.8) years. Fifty five per cent received co-trimoxazole, and 45% received placebo. A higher proportion of participants in the co-trimoxazole group than in the placebo group were malnourished (weight for age z score < -2) (P=0.06). No other significant differences in background data existed.

We defined a group with very good follow-up. This included 50 participants who had three or more visits within 10 days after inclusion.

Of participants who developed pneumonia or were admitted to hospital, one was from the co-trimoxazole group, and six were from the placebo group; four had been vaccinated against measles, and three were unvaccinated.

Laboratory confirmed measles

Among the 84 cases, 67 (80%) were serologically confirmed. Owing to inconsistencies in testing of the remaining 17 cases, we considered that all clinically diagnosed cases probably represented measles infection.

Treatment failure due to pneumonia or hospital admission

One of 46 participants taking co-trimoxazole developed pneumonia compared with six of 38 children taking placebo (odds ratio 0.08 (95% confidence interval 0 to 0.56), controlled for age group) (table 1). The number needed to treat was 7 (4 to 48). All three participants admitted to hospital had received placebo (P=0.09). Among 50 participants with very good follow-up, the odds ratio was 0.05 (0 to 0.47), adjusted for age group. Results were similar among 67 participants with laboratory confirmed measles (table 1).

Other outcome measures

Weight gains during the first month after inclusion were 15 (2 to 29) g per day in the placebo group and 32 (23 to 42) g per day in the co-trimoxazole group (P=0.04). A non-significant weight loss occurred in the 2-11 months age group in the co-trimoxazole group compared with the placebo group; in the other age groups a weight gain occurred, which was significant in the 5-17 years age group (table 2).

We found significantly less conjunctivitis and a non-significant tendency to less diarrhoea, oral thrush (P=0.09), severe fever, and stomatitis among recipients of co-trimoxazole. Otitis media did not differ between the groups (table 1). Forty four participants had no complications, 22 had one complication, eight had two, five had three, one had four, two had five, and two had seven complications. Among 40 participants with any complication, 21 had received placebo and 19 had received co-trimoxazole (odds ratio 0.47 (0.18 to 1.18), adjusted for age group). Eight participants in the placebo group had three or more complications, as did two in the co-trimoxazole group (P=0.04). Among participants with complications, 19 (48%) were vaccinated. Among 44 participants without complications, 25 (57%) were vaccinated. Vaccinated participants had a marginally lower risk of complications than unvaccinated ones (relative risk 0.82 (0.52 to 1.29)). The effect of co-trimoxazole was the same among vaccinated and unvaccinated participants (test for interaction, P=0.45).

Discussion

Participants with measles who received co-trimoxazole had less pneumonia, less conjunctivitis, and more weight gain than those who received placebo,

Table 2 Weight change per age group between co-trimoxazole and placebo groups

Age group	Weight change (g/day), adjusted†		
	Co-trimoxazole	Placebo	Co-trimoxazole – placebo (95% CI)
2-11 months (n=9)	9	26	-18 (-56 to 21)
1-2 years (n=9)	28	8	20 (-2 to 42)
3-4 years (n=17)	28	0	27 (-11 to 67)
5-17 years (n=40)	65	27	39 (10 to 68)*
All ages (n=75)	32	15	17 (1 to 33)*

*P<0.05.

†Adjusted for age group, weight for age at inclusion, time since rash, and measles vaccination status.

indicating a beneficial effect of prophylactic antibiotics in the management of measles in low income countries. The number needed to treat was 7, so for every seven patients with measles treated with prophylactic antibiotics one case of pneumonia was prevented.

Nutritional status

Our data show a benefit from receiving prophylactic antibiotics, an effect that might have been underestimated as a result of the uneven proportion of malnourished patients in the two groups. Overall, a significantly larger weight gain occurred in the co-trimoxazole group. Non-significant weight loss occurred among infants who received co-trimoxazole compared with placebo, which is a matter for concern.

Diagnosis of measles

Although 20% of the cases of measles were not confirmed serologically, all patients with measles had typical symptoms. The combination of the clinical picture, exposure to measles, and the serological tests gives a high likelihood of the diagnosis of measles being correct.

Strengths and weaknesses

The small sample size of 84 patients with measles is a serious limitation to this study. Even so, all but one case of pneumonia and all the hospital admissions occurred in the placebo group. This, combined with data showing significantly less conjunctivitis and a larger weight gain in the co-trimoxazole group, indicates a beneficial effect of prophylactic antibiotics. The risk of developing complications was 18% lower among vaccinated than unvaccinated participants. Once a patient had acquired measles, the effect of co-trimoxazole was the same among vaccinated and unvaccinated participants.

Several questions remain because of the limited study size. The study does not provide mortality results, as no participant died. If prophylactic antibiotics reduce the occurrence of measles associated pneumonia by about 90%, a reduction in mortality from measles would be expected.⁸ In the Senegalese study, case fatality rates fell twofold and respiratory symptoms threefold with the introduction of prophylactic antibiotics.⁴

Antibiotic resistance

Widespread resistance to co-trimoxazole exists,⁹ but no clear association exists between antimicrobial resistance and clinical outcome of pneumonia.¹⁰ If co-trimoxazole could prevent a large proportion of bacterial pneumonia and pneumonia related deaths it is probable that the strategy would be highly cost effective. Whether prophylactic treatment with co-trimoxazole will add to the development of resistance is questionable. Antimicrobial resistance to amoxicillin is less common, and amoxicillin may be an alternative to co-trimoxazole.

Conclusions

Even though a Cochrane review concluded that antibiotics should be given only if clinical signs of pneumonia or other evidence of sepsis are present,^{3 11} we believe that the evidence favours the use of prophylactic antibiotics in measles in low income countries. Prophylactic antibiotics should be used in patients with

What is already known on this topic

Studies of prophylactic antibiotics in measles have been inconclusive when evaluated by current standards

An observational study from Senegal found a twofold reduction in measles case fatality rate and a threefold reduction in respiratory symptoms with prophylactic antibiotics

What this study adds

Prophylactic antibiotics in measles infection prevented pneumonia, conjunctivitis, and possibly other complications and improved weight gain in the month after measles infection in a low income setting

measles, disregarding vaccination status, in settings with a high risk of complications when the diagnosis of measles is quite certain, such as during epidemics. Further trials might examine different drug regimens and their impact in different age groups, patterns of antibiotic resistance, and mortality from measles to get an idea if the case fatality rate declines.

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