

THIS WEEK'S RESEARCH QUESTIONS

- 808** What is the efficacy and safety of bronchodilators and steroids in acute management of bronchiolitis?
809 How effectively does co-trimoxazole prophylaxis protect against malaria in HIV uninfected children born to HIV infected mothers in Africa?
810 Do statins protect against all cause mortality after a diagnosis of pneumonia?
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Malaria prophylaxis with co-trimoxazole in children exposed to HIV



More than two million infants are born to HIV infected African mothers each year, and the World Health Organization recommends giving these infants

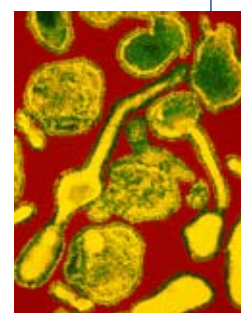
co-trimoxazole prophylaxis until breast feeding (and exposure to HIV) ends and HIV infection is excluded. The prophylaxis protects HIV infected children from common opportunistic infections, including malaria. More than 90% of these infants remain uninfected throughout breast feeding, but this cannot easily be confirmed because maternal HIV antibodies persist in infant blood until 18 months of age. Thus, many of these children continue taking co-trimoxazole prophylaxis until antibody testing for HIV infection becomes possible.

This led Taylor Sandison and colleagues to conduct a randomised clinical trial (p 809) of co-trimoxazole prophylaxis against malaria in such HIV exposed, uninfected children in rural Uganda, where both malaria transmission intensity and resistance to antimalarial antifolate drugs are high. (They used the polymerase chain reaction to confirm absence of HIV DNA in the children, but that's not readily available in rural Africa.) Continuing daily prophylaxis after end of breast feeding to 2 years of age decreased the incidence of malaria by 39% compared with stopping prophylaxis at the end of breast feeding. One big question, discussed in the full article, is why the protective efficacy of co-trimoxazole against malaria in this trial was so much lower than in other studies (with reports of 80-99% efficacy).

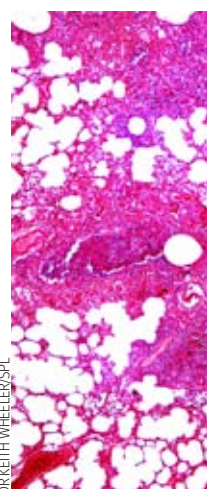
Steroids and bronchodilators for acute bronchiolitis in babies and toddlers

Doctors and patients often need to consider a wide range of treatments with different outcomes. Searching for robust evidence of which one is best will often yield only a single meta-analysis of treatment A versus treatment B or placebo, which may not do much to guide decision making in the real world. Increasingly, therefore, researchers are using complex methods to combine several systematic reviews on the same condition and to analyse outcome data for all relevant treatment comparisons. That's what Lisa Hartling and colleagues have done in their systematic review and Bayesian network meta-analysis of bronchodilators and steroids, alone or combined, in the acute management of bronchiolitis in patients aged 24 months or less (p 808). Previous studies have shown that this condition is treated in many different ways round the world, but here nebulised adrenaline given in the emergency department proved the best way to keep patients out of hospital on day 1, while combined nebulised adrenaline and oral dexamethasone most effectively reduced admission rates over the next week.

A couple of weeks ago we published a letter from Valeria Fadda and colleagues explaining how a single figure can show the comparative effectiveness of various treatments in a network meta-analysis (doi:10.1136/bmj.d1555). This paper on bronchiolitis comes with just such a figure.



Statin treatment after pneumonia



Two years ago a systematic review of observational studies suggested that statins might protect against sepsis and mortality (<http://bit.ly/hOcQMe>). At around the same time Liam Smeeth and colleagues reported a cohort study using The Health Improvement Network (THIN) database of UK computerised primary care records, which suggested that statins might protect against pneumonia (doi:10.1111/j.1365-2125.2008.03308.x). Building on that work, Smeeth and colleagues have now looked at mortality in the six months after diagnosis of pneumonia among patients aged over 40 who were either users of statins (109/847; 13% died) or matched non-users (578/2927; 20% died) (p 810).

The authors used modelling and a propensity score based method to control for differences between people prescribed and not prescribed statins. Given the inability of an observational study to completely rule out confounding and other biases, however, the authors say it is now time for a randomised controlled trial to test the association. They estimate, cautiously, that their result would equate to a trial derived number needed to treat (to prevent death within six months of an episode of pneumonia) of 15. In the meantime, this study—in which the main analysis covered nearly 5000 episodes of pneumonia with around 1000 in patients prescribed statins—provides much food for thought.

LATEST RESEARCH: For these and other new research articles see www.bmj.com/research

Effectiveness of antenatal corticosteroids in reducing respiratory disorders in late preterm infants A randomised controlled trial by Ana Maria Feitosa Porto and colleagues showed that antenatal treatment with corticosteroids at 34-36 weeks of pregnancy did not reduce the incidence of respiratory disorders in newborn infants (doi:10.1136/bmj.d1696).

Reporting of eligibility criteria of randomised trials Anette Blümle and colleagues found that the eligibility criteria reported in published articles differed from those given in the protocol for all 52 of the trials they looked at (doi:10.1136/bmj.d1828).

Understanding provision of chemotherapy to patients with end stage cancer The findings of Hilde Buiting and colleagues' qualitative study suggest that doctors may offer further chemotherapy to patients with end stage cancer out of the fear that "giving up hope" will harm their wellbeing (doi:10.1136/bmj.d1933).

EDITORIAL by Ducharme

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Steroids and bronchodilators for acute bronchiolitis in the first two years of life: systematic review and meta-analysis

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STUDY QUESTION

What is the efficacy and safety of bronchodilators and steroids, alone or combined, in the acute management of bronchiolitis?

SUMMARY ANSWER

Evidence shows the effectiveness and superiority of adrenaline (epinephrine) for outcomes of most clinical relevance among outpatients with acute bronchiolitis, and evidence from a single precise trial for combined adrenaline and dexamethasone.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

The management of acute bronchiolitis varies substantially throughout the world, including the use of different bronchodilators and steroids. Evidence shows a benefit of adrenaline in reducing admission rates from the emergency department on day 1, and suggests a benefit of combined adrenaline and dexamethasone for reducing admission rates up to seven days after the emergency department visit.

Selection criteria for studies

We searched Medline, Embase, Central, Scopus, PubMed, LILACS, and IranMedEx in November 2009, as well as conference proceedings and trial registers for randomised controlled trials of children aged 24 months or less with a first episode of bronchiolitis with wheezing comparing any bronchodilator or steroid, alone or combined, with

placebo or another intervention (other bronchodilator, other steroid, standard care).

Primary outcome(s)

Primary outcomes were selected by clinicians a priori based on clinical relevance: rate of admission for outpatients (days 1 and 7) and length of stay for inpatients.

Main results and role of chance

Forty eight trials (4897 patients, 13 comparisons) were included. The drugs were administered in a variety of ways and varied across studies and interventions: corticosteroids—systemic (oral, intravenous, or intramuscular) or nebulised; adrenaline—nebulised; and bronchodilators—mostly nebulised. Risk of bias was low in 17% of the studies (n=8), unclear in 52% (n=25), and high in 31% (n=15). Only adrenaline reduced admissions on day 1 (compared with placebo: pooled risk ratio 0.67, 95% confidence interval 0.50 to 0.89; number needed to treat (NNT) 15, 95% confidence interval 10 to 45 for a baseline risk of 20%; 920 patients). Unadjusted results from a single large trial with low risk of bias showed that combined dexamethasone and adrenaline reduced admissions on day 7 (risk ratio 0.65, 0.44 to 0.95; NNT=11, 7 to 76 for a baseline risk of 26%; 400 patients). A mixed treatment comparison supported adrenaline alone or combined with steroids as the preferred treatments for outpatients (probability of being the best treatment based on admissions at day 1 were 45% and 39%, respectively). None of the interventions examined showed clear efficacy in terms of length of stay among inpatients; however, limited evidence suggested some benefits in clinical score for adrenaline versus salbutamol (at 60 and 120 minutes), as well as steroids versus placebo (at 3-6 hours and 6-12 hours) and salbutamol or terbutaline versus placebo (at 6-12 hours). In general the incidence of adverse effects was low and no important differences were observed between study groups. No studies examined, or were necessarily designed to examine, long term adverse effects.

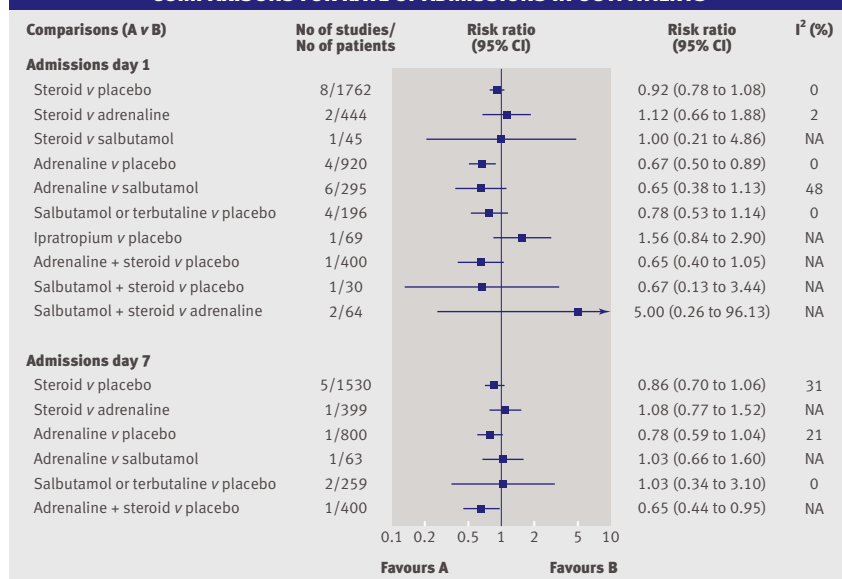
Bias, confounding, and other reasons for caution

The strength of evidence was affected by potential risk of bias in the included studies and sparsity of data for many of the outcomes and comparisons, which resulted in imprecise estimates and unknown consistency of estimates across studies.

Study funding/potential competing interests

This research was supported by the Canadian Institutes of Health Research knowledge synthesis grant programme. The funding agency was not involved with the study design or collection, analysis, and interpretation of the data. DJ, AP, and TPK are authors of one or more randomised controlled trials included in this work.

RESULTS FROM META-ANALYSIS OF DIRECT COMPARISONS FOR RATE OF ADMISSIONS IN OUTPATIENTS



Protective efficacy of co-trimoxazole prophylaxis against malaria in HIV exposed children in rural Uganda: a randomised clinical trial

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- Disappearance of drugs undermines Uganda's fight against malaria (*BMJ* 2010;340:c2611)
- Uganda runs out of antiretroviral drugs after shortfall in aid (*BMJ* 2009;339:b3255)
- Meeting information needs of patients with incurable progressive disease and their families in South Africa and Uganda: multicentre qualitative study (*BMJ* 2009;338:b1326)
- Combination antiretroviral therapy in population affected by conflict: outcomes from large cohort in northern Uganda (*BMJ* 2009;338:b201)

STUDY QUESTION

How effectively does co-trimoxazole prophylaxis protect against malaria in HIV exposed children (uninfected children born to HIV infected mothers) in Africa?

SUMMARY ANSWER

When continued beyond the period of HIV exposure (during breast feeding) up to 2 years of age, co-trimoxazole prophylaxis was moderately protective against malaria (39% lower incidence) in an area with high malaria transmission intensity and a high prevalence of antifolate resistance.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Observational studies of daily co-trimoxazole prophylaxis in children and adults have found a protective efficacy of 80% and higher against malaria. This is the first randomised controlled trial investigating the protective efficacy of co-trimoxazole prophylaxis against malaria in HIV exposed children.

Design

In this non-blinded, randomised controlled trial participants were prescribed co-trimoxazole prophylaxis from enrolment until cessation of breast feeding and exclusion of HIV infection (by testing for HIV DNA by polymerase chain reaction). Uninfected children were then randomised to stop co-trimoxazole prophylaxis immediately or to continue it until 2 years of age.

Participants and setting

A total of 203 breastfeeding, HIV exposed infants were enrolled between 6 weeks and 9 months of age in Tororo District of Uganda—a rural area of high malaria transmission intensity and high prevalence of *Plasmodium* genotypes associated with antifolate resistance. At cessation of breast feeding, 185 remained HIV uninfected and were randomised to stopping co-trimoxazole prophylaxis (n=87) or continuing co-trimoxazole (n=98).

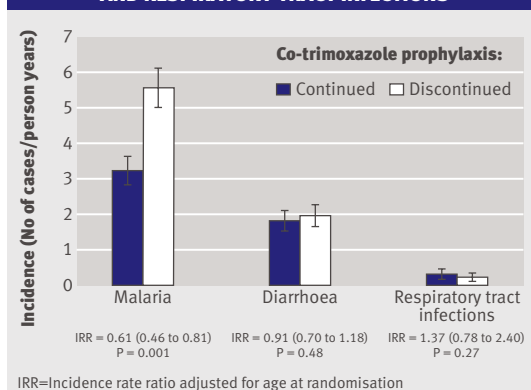
Primary outcome

Incidence of malaria was calculated as the number of antimalarial treatments per person year at risk.

Results

The incidence of malaria and prevalence of genotypic mutations associated with antifolate resistance were high throughout the study. From the time of randomisation until each participant reached 2 years of age, the incidence of malaria was 3.24 episodes/person year (95% CI 2.89 to 3.63) among participants who continued co-trimoxazole prophylaxis and 5.57 episodes/person year (5.04 to 6.14) among those who stopped co-trimoxazole, representing a 39% lower risk of malaria with continued co-trimoxazole to 2 years of age (incidence rate ratio 0.61 (95% CI 0.46 to 0.81), $P=0.001$). There were no significant differences in the incidence of

PROTECTIVE EFFICACY OF CO-TRIMOXAZOLE PROPHYLAXIS AGAINST MALARIA, DIARRHOEA, AND RESPIRATORY TRACT INFECTIONS



complicated malaria, diarrhoea, pneumonia, adverse events (including skin reactions, neutropenia, and anaemia), hospitalisations, or deaths between the two study arms.

Harms

There were no deaths, hospitalisations, or adverse events with permanent sequelae resulting from the continued use of co-trimoxazole prophylaxis.

Bias, confounding, and other reasons for caution

There were no significant differences between the two study arms in baseline characteristics, and 92% of the participants randomised to the two arms remained available for analysis at 2 years of age. A potential source of bias was the repeated measures among the same individuals (699 episodes of malaria in total among 150 children), but we accounted for this in our analyses.

Generalisability to other populations

The degree of protection from co-trimoxazole prophylaxis against malaria in our trial was substantially lower than that reported in observational studies. Our results may have been influenced by the high malaria transmission intensity and high prevalence of antifolate resistance genotypes found in eastern Uganda, as well as the HIV exposure and younger age of the children enrolled in our trial. Consequently, our results may not reflect the protective efficacy of co-trimoxazole against malaria in other settings.

Study funding/potential competing interests

Funding was provided through the US President's Emergency Plan for AIDS Relief, Centers for Disease Control and Prevention (CDC), the Doris Duke Charitable Foundation, Puget Sound Partners in Global Health, and National Institute of Allergy and Infectious Diseases (NIAID).

Trial registration Clinical Trials NCT00527800

Effect of statin treatment on short term mortality after pneumonia episode: cohort study

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STUDY QUESTION

Do statins protect against all cause mortality after a diagnosis of pneumonia?

SUMMARY ANSWER

The risk of death in the six month period after diagnosis of pneumonia was substantially lower among people who were already receiving a statin compared with people not receiving a statin.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Clinical studies and laboratory work suggest that use of statins may be associated with a more favourable outcome after bacterial infection. This study supports a possible protective effect of statins against mortality in people with pneumonia and suggests that a randomised clinical trial is warranted to investigate this further.

Participants and setting

We did this study in The Health Improvement Network (THIN), a database of computerised medical records of general practices in the United Kingdom. We identified a study population of all statin users aged over 40 years at first prescription of a statin between 1 January 1995 and 31 December 2006 and matched each statin user on age, sex, practice, and calendar period with up to five non-statin users.

Design, size, and duration

From the study population (129 288 statin users; 600 241 non-statin users), we selected all patients with a record of pneumonia and followed them for six months to see if they died. We calculated propensity scores to help to identify statin users and non-users who could be fairly compared and to allow adjustment for confounding. We used multivariate Cox regression to compare the rate of death in people receiving statins (n=847) at the time pneumonia occurred with that of people not receiving statins (n=2927), excluding patients who died on the day pneumonia was diagnosed.

Main results and the role of chance

The rate of death in the six months after diagnosis of pneumonia was substantially lower among statin users

(109/847; 13%) than in non-statin users (578/2927; 20%). The fully adjusted rate ratio for mortality was 0.67 (95% confidence interval 0.49 to 0.87). With all time periods included, the rate ratio for mortality comparing statin users with non-users regardless of pneumonia status was 0.82 (0.79 to 0.86). This suggests that statins have a protective effect during the time after an episode of pneumonia over and above their established benefits.

Bias, confounding, and other reasons for caution

Although we made strenuous efforts to minimise confounding, including restricting analyses to comparable patients, we cannot exclude the possibility that unknown differences between statin users and non-users could have contributed to the results. Other possible biases, such as misclassification of statin status or death, are plausible but would most likely lead to an underestimate of any treatment effect. We studied patients already established on statin treatment when they developed pneumonia; for the results to change clinical practice, we would need to determine whether starting a statin at the time of diagnosis has a similar effect. This could be done in a randomised clinical trial.

Generalisability to other populations

We did the study in the general adult population of the UK, and the results are likely to be widely applicable in other settings.

Study funding/potential competing interests

The study was funded by the Wellcome Trust and the Medical Research Council.

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ASSOCIATION BETWEEN USE OF STATIN AND MORTALITY

Outcome	No of patients	No (%) deaths	Age and sex adjusted effect estimate: hazard ratio (99% CI)	Fully adjusted effect estimate: hazard ratio (99% CI)
Mortality within 6 months of pneumonia, excluding deaths on day of pneumonia				
Did not use statin	2 927	578 (20)	—	—
Used statin	847	109 (13)	0.62 (0.47 to 0.81)	0.67 (0.49 to 0.91)
All mortality after index date (regardless of pneumonia status)				
Did not use statin	308 730	32 445 (11)	—	—
Used statin	51 397	4 718 (9)	0.95 (0.91 to 0.99)	0.82 (0.79 to 0.86)

Statin treatment for primary prevention of vascular disease: whom to treat? Cost-effectiveness analysis

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STUDY QUESTION What is the cost effectiveness of low dose statins for primary prevention of vascular disease with incorporation of current statin prices and non-adherence.

SUMMARY ANSWER In daily practice, statin treatment appeared not to be cost effective for low risk primary prevention populations.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Statin treatment reduce the risk of major cardiovascular and cerebrovascular events in people without established cardiovascular disease. Statin treatment seemed not to be cost effective for low risk primary prevention populations, despite low costs of generic drugs. Improved adherence to statins might enhance cost effectiveness.

Main results

Over a 10 year period, statin treatment costs €35 000 (£30 000, \$49 000) per quality adjusted life year (QALY) gained for Dutch men aged 55 years with a 10 year vascular risk of 10%. The incremental cost-effectiveness ratio improved as risk for vascular disease increased. The cost per QALY ranged from approximately €5000 to €125 000 when the 10-year vascular risk for men aged 55 years was varied from 25% to 5% (table). The incremental cost effectiveness ratio slightly decreased with age after the level of vascular risk was specified. The predicted health benefits were somewhat lower in women than in men, which resulted in slightly higher incremental cost effectiveness ratios.

Design

Cost effectiveness analysis with a Markov model. Sensitivity analyses and Monte Carlo simulation evaluated robustness of the results. The time horizon was 10 years.

Source(s) of effectiveness

A meta-analysis of 10 randomised controlled trials of statins for primary prevention was the key source of data for clinical efficacy. Real world adherence rates were derived

from published literature. Incidence and case fatality rates for myocardial infarction, stroke, myopathy, and rhabdomyolysis were obtained from published studies. To deal with gaps in the data, several assumptions were made, such as that the risk ratios were constant across age groups.

Data sources

The direct medical costs were those of drug treatment, doctors' visits, and event related and ongoing costs such as hospital admissions, surgery, rehabilitation, and nursing home admissions. Annual costs were derived from Dutch or European published cost studies. Utilities were derived from the literature.

Results of sensitivity analysis

Results were sensitive to the costs of statin treatment, statin effectiveness, non-adherence, disutility of taking medication daily, and the time horizon of the model.

Limitations

Sensitivity analysis showed that modelling over a person's lifetime, rather than 10 years, would lead to more favourable cost effectiveness results, especially for younger people. However, treatment started in such individuals would be difficult to continue over their lifetimes. Secondly, the low costs of statins in the Netherlands, as used in this study, are not achievable in most countries; higher costs would strengthen our conclusion that the drugs have a limited role in primary prevention. Thirdly, our economic analysis was from the healthcare payer's perspective (only direct medical costs included). If indirect costs representing loss of productivity were included, statin treatment would be more cost effective.

Study funding/potential competing interests

The study was funded by the Netherlands Organization for Health Research and Development. The department of FLV has received research grants from Merck, the Netherlands Organisation for Health research and Development and from the Catharijne foundation Utrecht and speaker fees from Merck and AstraZeneca.

ESTIMATED DIFFERENCE IN MEAN COSTS AND QUALITY-ADJUSTED LIFE EXPECTANCY OF STATIN TREATMENT IN DUTCH MEN OVER A 10 YEAR PERIOD

Age (years)	10 year vascular risk (%)	Absolute risk reduction (%)	Incremental costs (€)	Incremental QALYs	ICER (€ per QALY)
45	2.5	0.4	916	-0.001	NA
	7.5	1.0	781	0.010	78 136
	15.0	2.0	584	0.027	21 651
55	2.5	0.4	898	0.000	NA
	10.0	1.4	702	0.020	34 995
	25.0	3.2	324	0.060	5 395
65	5.0	0.7	787	0.010	75 237
	15.0	2.0	558	0.044	12 652
	25.0	3.1	334	0.077	4 319

ICER=incremental cost effectiveness ratio, NA=not applicable