RESEARCH

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RYAN BROOKES

THIS WEEK'S RESEARCH QUESTIONS

153 What is the role of scorpion antivenom in the management of severe *Mesobuthus tamulus* sting in a rural setting?

154 What is the cardiovascular safety of non-steroidal anti-inflammatory drugs?

155 What are the frequency and reasons for outcome reporting bias in clinical trials?

156 What are the cost, cost effectiveness, and sex equity of different intervention strategies within the English National Chlamydia Screening Programme?

Treatment for scorpion sting in rural India

Bawaskar and Bawaskar's randomised head to head trial on treating scorpion sting in rural India is not a typical *BMJ* paper (p 153). But editorialists Edward Mills and Nathan Ford highlight its worth as "a reminder that global health researchers often neglect conditions that matter to large impoverished communities" (p 115).

Faced with *Mesobuthus tamulus* sting as a common and potentially life threatening presentation in their rural practice, the researchers tried to clarify the role of treatment with scorpion antivenom. They found that when used in combination with the standard treatment, prazosin, antivenom greatly shortened patients' recovery times compared with prazosin alone.

The preliminary, specialised, and localised nature of the research might have ruled it out for publication in the *BMJ*, but reviewers and editors were impressed by the trialists' efforts to address an important public health problem with very limited resources. A shortcoming was that the primary outcome, time to recovery, was a subjective one assessed by the (unblinded) investigators themselves. But this was the best available option under the circumstances, and certainly not a simple one to implement—the researchers sat by victims' bedsides for hours monitoring symptoms.

Given the importance of this problem to some readers, and its paradoxical neglect—which may in part explain why antivenom remains expensive and inaccessible—we concluded that the findings deserved an audience. We also allowed the researchers to register the trial retrospectively (http://tiny.cc/jbahb): when they started the trial Clinical Trials Registry-India didn't exist and the authors weren't aware of international journals' requirements for registration.

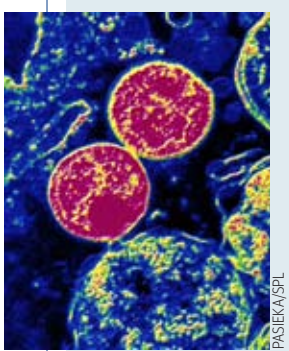
Biased reporting of outcomes in clinical trials

Many journals, including the *BMJ*, will welcome a trial with "negative" results as long as the study is robust and adequately powered. Avoiding bias against such studies helps to balance the evidence base, and it may be important to know that an intervention didn't work.

Editors' decisions are not, however, the only cause of publication bias; authors also skew the scientific record by failing to report fully all the study outcomes they had planned to measure. Rosalind Smyth and colleagues contacted authors of 268 randomised controlled trials (183 identified in Cochrane systematic reviews as probably reporting outcomes in a biased way and a further 85 randomly selected from PubMed; p 155). In all, 161 authors replied and, eventually, 59 took part in phone interviews to discuss the reporting of their work in protocols and papers. More than a quarter said that they had analysed but chosen not to report some prespecified trial outcomes, and in all but one case this made the conclusions more positive than they should have been. It was just as common to measure and then not analyse some outcomes.

Smyth and colleagues found only one case of outright manipulation, however, and mostly attribute the rest to researchers' lack of awareness that they should report everything accurately and fully. Their own study's low response rate introduces some bias too, but it's unlikely that only the responders had something to admit.

Sven Trelle and colleagues' network meta-analysis of the cardiovascular safety of seven non-steroidal anti-inflammatory drugs came up against the same problem (p 154). They analysed unpublished data for the trials of celecoxib and lumiracoxib, but were denied access to unpublished safety data from trials of rofecoxib and etoricoxib. Many of the included outcome data were reported incompletely and erratically, with important discrepancies in the reported number of events between different sources of information for major trials. Naproxen seemed least harmful but the authors warn that "evidence is lacking to suggest that any of the investigated drugs are safe in cardiovascular terms."



PASIEKA/SPL

Improving chlamydia screening for men

In England, twice as many women are screened for chlamydia as men (http://bit.ly/hhGGeB). Katy Turner and colleagues have modelled data reported by the National Chlamydia Screening Programme in 2008-9 to determine how best to tackle this gender inequity—either by increasing coverage of primary screening in men or increasing the efficacy of partner notification (p 156).

Increasing male coverage of screening to the same level as female coverage caught almost 40 000 extra cases, whereas doubling the efficacy of partner notification picked up far fewer: around 19 000 additional diagnoses. However, upping partner notification reduced the cost per infection treated by £57, but higher male coverage increased the cost by £22. Increasing the efficacy of partner notification also reduced the sex ratio (female:male) of treatment of infected individuals from 2.0:1 to 1.4:1.

Overall, improving the efficacy of partner notification would add an extra £3.3m to the £46.3m cost of the programme, compared with a further £22.9m if screening of men was increased. The authors conclude that: "the additional resources required to increase male screening coverage to reach equity with females would be more effectively employed in achieving high partner notification efficacy among those who test positive."

Efficacy and safety of scorpion antivenom plus prazosin compared with prazosin alone for venomous scorpion (*Mesobuthus tamulus*) sting: randomised open label clinical trial

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Cite this as: *BMJ* 2010;341:c7136
doi: 10.1136/bmj.c7136

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;341:c7136

STUDY QUESTION

What is the role of scorpion antivenom in the management of severe *Mesobuthus tamulus* sting in a rural setting?

SUMMARY ANSWER

Scorpion antivenom plus prazosin hastened recovery compared with prazosin alone.

WHAT IS KNOWN AND WHAT THIS STUDY ADDS Prazosin is a known and easily available antidote to *Mesobuthus tamulus* venom action. Antivenom against this venom has recently become available, but no scientific
clinical data are available. We found that addition of scorpion antivenom to prazosin enhanced recovery and shortened the hospital stay.

Design

Randomised open label trial of scorpion antivenom plus prazosin (n=35) compared with prazosin alone (n=35). Treatment was assigned by block randomisation.

Participants and setting

Seventy patients admitted to our general hospital in rural India with grade 2 scorpion sting; older than six months with no cardiorespiratory or central nervous system abnormalities.

Primary outcome

Clearing of syndrome (including profuse sweating, ropy salivation, priapism, hypotension or hypertension, bradycardia or tachycardia, and cold extremities) within 10 hours of treatment.

Main results and the role of chance

Thirty-two patients (91.4%, 95% confidence interval 76.9% to 97.8%) in the prazosin plus antivenom group showed complete resolution of the clinical syndrome within 10 hours of treatment, compared with eight in the prazosin group (22.9%, 11.8% to 39.3%). Patients given antivenom plus prazosin recovered earlier (mean 8 hours, 95% CI 6.5 to 9.5) than those given prazosin alone (17.7 hours, 15.4 to 19.9; mean difference −9.7 hours, −6.9 to −12.4). The proportion of patients whose condition deteriorated to a higher grade was similar in both groups (antivenom plus prazosin n=4, prazosin alone n=5).

Harms

No participant had a mild or severe reaction to antivenom.

Bias, confounding and other reasons for caution

This study was not blinded, and the primary outcome was evaluated by the study investigators, who had extensive clinical experience with scorpion sting. Assessment of symptom clearance was thus subjective, but we think that this was a clinically relevant and pragmatic way of judging effects of treatment in a trial carried out in challenging circumstances with restricted resources.

Generalisability to other populations

Our results would be applicable in settings such as primary health centres, where most patients with scorpion sting first present. We could not enrol patients with grade 3 and 4 severe scorpion stings owing to restriction by the ethics committee.

Study funding/potential competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Trial registration number

CTRI/2010/091/000584 (Clinical Trials Registry India).

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One of the authors discusses this research paper in a *BMJ* podcast at bmj.com/podcasts

RECOVERY TIME FOR CLINICAL SYNDROME

Clinical sign	Prazosin (n=35)	Prazosin plus antivenom (n=35)	P
Sweating, mean (SD) hours	6.6 (2.6)	3 (1.1)	<0.001
Salivation, mean (SD) hours	3.0 (1.9)	1.9 (.9)	0.008
Priapism, mean (SD) hours	9.4 (1.5) (n=24)	4.7 (1.5) (n=27)	<0.001
Cold extremities, mean (SD) hours	17.3 (6.6)	8.5 (5.3)	<0.001
Number (%) with hypotension	19 (54.3%)	12 (34.3%)	<0.001

Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis

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Cite this as: *BMJ* 2011;342:c7086
doi: 10.1136/bmj.c7086

This is a summary of a paper that was published on bmj.com as *BMJ* 2011;342:c7086

STUDY QUESTION

What is the cardiovascular safety of non-steroidal anti-inflammatory drugs?

SUMMARY ANSWER

Although uncertainty remains, evidence is lacking to suggest that any of the investigated drugs are safe in cardiovascular terms. However, naproxen seemed least harmful.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Several standard meta-analyses were not able to resolve the debate about the cardiovascular safety of cyclo-oxygenase-2 selective inhibitors and traditional non-steroidal anti-inflammatory drugs because they failed to integrate all available randomised evidence in one analysis. According to the present analysis, safety profiles of individual drugs varied considerably depending on the outcome. Estimated rate ratios for comparisons with placebo were generally imprecise, but naproxen seemed least harmful among the seven drugs analysed.

Selection criteria for studies

From bibliographic databases, the Food and Drug Administration website, and study registers we identified randomised trials with at least 100 patient years of follow-up per trial arm that compared non-steroidal anti-inflammatory drugs head to head or against placebo.

Primary outcomes

The prespecified primary outcome was fatal or non-fatal myocardial infarction. Secondary outcomes were stroke, cardiovascular death, any death, and a composite of cardiovascular events and death.

Main results and role of chance

Thirty one trials in 116 429 patients and with more than 115 000 patient years of follow-up were included. Patients were allocated to naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib, lumiracoxib, or placebo. Compared with placebo, rofecoxib was associated with the highest risk of myocardial infarction (rate ratio 2.12, 95% credibility interval 1.26 to 3.56), followed by lumiracoxib (2.00, 0.71 to 6.21). Ibuprofen was associated with the highest risk of stroke (3.36, 1.00 to 11.6), followed by diclofenac (2.86, 1.09 to 8.36). Etoricoxib (4.07, 1.23 to 15.7) and diclofenac (3.98, 1.48 to 12.7) were associated with the highest risk of cardiovascular death.

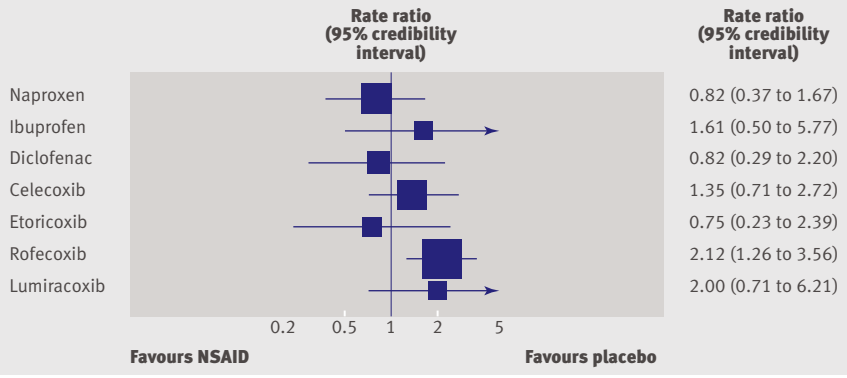
Bias, confounding, and other reasons for caution

Network meta-analysis makes similar assumptions to standard meta-analysis of direct comparisons within trials but requires that these assumptions hold over the entire set of trials in the network—that is, for the indirect comparisons also. Although these assumptions were met, the tests used to evaluate the assumptions had low power. Although more than 115 000 patient years of follow-up were included in the analyses, the number of events for most outcomes was low and our estimates of rate ratios imprecise, as indicated by wide credibility intervals.

Study funding/potential competing interests

SR, ME, and PJ received grants (Nos 4053-40-104762/3 and 3200-066378) from the Swiss National Science Foundation's national research programme 53 on musculoskeletal health. PJ was a programme for social medicine, preventive and epidemiological research senior research fellow funded by the Swiss National Science Foundation (grant No 3233-066377). CTU Bern is supported by the Swiss National Science Foundation.

ESTIMATED RATE RATIOS OF MYOCARDIAL INFARCTIONS FOR NON-STEROIDAL ANTI-INFLAMMATORY DRUGS COMPARED WITH PLACEBO



Frequency and reasons for outcome reporting bias in clinical trials: interviews with trialists

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EDITORIAL by Chan
BLOG p 135
ANALYSIS p 148

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Cite this as: *BMJ* 2010;341:c7153
doi: 10.1136/bmj.c7153

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;341:c7153

STUDY QUESTION

What are the frequency and reasons for outcome reporting bias in clinical trials?

SUMMARY ANSWER

The prevalence of incomplete outcome reporting is high, and trialists seem generally unaware of the implications for the evidence base of not reporting all outcomes and protocol changes.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Outcome reporting bias is a threat to evidence based medicine because trial outcomes with statistically significant results are more likely to be published. This study has provided a detailed understanding of why trialists do not report previously specified outcomes. A lack of consensus regarding choice of outcomes in particular clinical settings was evident in this study.

Rationale, design, and data collection method

This study was performed in two parts: trial protocols were compared with subsequent publication(s) to identify any discrepancies in the reported outcomes; and telephone interviews were conducted with the respective trialists to investigate more extensively the reporting of the research.

Participants and setting

Chief investigators, or lead or coauthors, from Australia, Canada, Germany, the Netherlands, New Zealand, the United Kingdom, and the United States were recruited.

Recruitment and sampling strategy

Eligible trialists were identified from two sources: trials published since 2002 covered in Cochrane systematic reviews where at least one included trial was suspected of being at risk of outcome reporting bias and a random sample of reports indexed on PubMed between August 2007 and July 2008. A total of 85 investigators from trials that were included in a Cochrane review and were suspected of outcome reporting bias for the review primary outcome were invited to be interviewed, as were 98 trialists from trials in the same Cochrane reviews that were considered not to show outcome reporting bias and 85 trialists from the randomly selected cohort of PubMed trials.

Data analysis method

Interviews were tape recorded, transcribed, and anonymised. Reasons provided by the trialists for not reporting prespecified outcomes were classified. A reporting practice was deemed to be associated with bias if the reason for non-reporting was related to the results obtained.

Main findings

Initially, 161 investigators responded to our requests for interview, 59 (37%) of whom were eventually interviewed. In almost all trials in which prespecified outcomes had been analysed but not reported (15/16, 94%), this underreporting resulted in bias. In nearly a quarter of trials in which prespecified outcomes had been measured but not analysed (4/17, 24%), the "direction" of the main findings influenced the investigators' decision not to analyse the remaining data. Reasons given by the trialists for not reporting outcomes are shown in the table.

There was at least one unreported efficacy or harm outcome in 14 (67%) of the 21 randomly selected PubMed trials. More than a quarter (6/21, 29%) of these trials were found to have displayed outcome reporting bias.

Implications

Our findings suggest that for assessment of reporting bias, reliance on comparing the protocol and publications without contacting trial authors will often be inadequate. We found a lack of understanding among investigators of the importance of reporting outcomes, which lends support to the development of core outcome sets.

Bias, limitations, and generalisability

The results presented come only from those trialists who agreed to be interviewed, and thus we urge caution in the interpretation of our study findings given the low response rate. The frequencies of various discrepancies in reporting were calculated using only data from the randomly selected cohort identified from PubMed.

Study funding and potential competing interests

This study was part of the larger Outcome Reporting Bias in Trials (ORBIT) project, which was funded by the Medical Research Council (grant number G0500952). DGA is supported by Cancer Research UK. The authors declare no competing interests.

INDICATIONS OF BIAS IN RESPONSES FROM TRIALISTS WHO HAD ANALYSED DATA ON A PRESPECIFIED OUTCOME BUT NOT REPORTED THEM BY THE TIME OF THE PRIMARY PUBLICATION

Trialist	Explanation from trialist
09	"It was just uninteresting and we thought it confusing so we left it out. It didn't change, so it was a result that we . . . you know, kind of not particularly informative let's say, and was to us distracting and uninteresting."
30	"When we looked at that data, it actually showed an increase in harm amongst those who got the active treatment, and we ditched it because we weren't expecting it and we were concerned that the presentation of these data would have an impact on people's understanding of the study findings. So we buried it. I think if I was a member of the public I would be saying 'what you are promoting this intervention you thought it might harm people—why aren't you telling people that?'"
32	"If we had a found a significant difference in the treatment group we would have reported that, and it certainly would have been something we probably would have been waving the flag about."
56	"I actually disagree that this outcome is important, but that was probably a more pragmatic aspect of making sure that our protocol was funded, because I think some reviewers might have said, 'wow you are not measuring this outcome!' That said, there is a vast amount of literature showing that it's of completely no relevance but it was a practical decision to make sure we got money. Once we conducted the study and reflected on our results more we just didn't think it had that much validity in telling us very much about the condition. So for the sake of brevity we didn't report that. I didn't expect there would be much of a difference, and our results show that there wasn't much of a difference."

Costs and cost effectiveness of different strategies for chlamydia screening and partner notification: an economic and mathematical modelling study

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Cite this as: *BMJ* 2010;341:c7250
doi: 10.1136/bmj.c7250

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;341:c7250

STUDY QUESTION What is the cost and effectiveness of different intervention strategies in a chlamydia screening programme?

SUMMARY ANSWER Within the English National Chlamydia Screening Programme increasing screening coverage in men to match that for women would cost over six times as much as doubling partner notification but only treat twice as many additional infections.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Partner notification is an essential component of a screening programme, as partners of those with chlamydia infection are likely to be infected too. Increasing the effectiveness of partner notification is likely to cost less than improving sex equity in screening coverage but also improve the ratio of women to men diagnosed and will reduce the cost per infection treated.

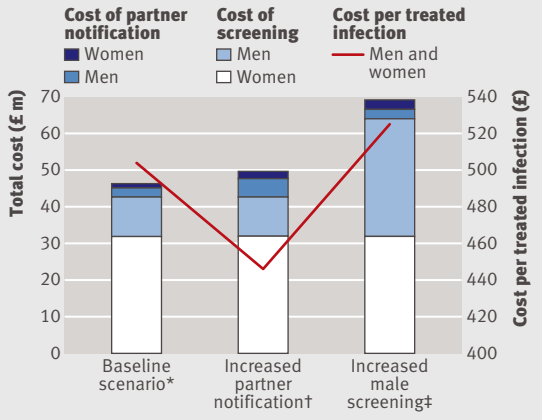
Design

We developed a spreadsheet model to examine the cost effectiveness of the National Chlamydia Screening Programme in 2008–9 (as cost per individual tested, cost per positive diagnosis, total cost of screening, number screened, number infected, and sex ratio of those tested and treated). We compared the baseline programme with two different interventions—(i) increased coverage of primary screening in men to give equal coverage of men and women and (ii) increased efficacy of notification of partners of index cases.

Data sources

National Chlamydia Screening Programme costing guidance initiative in England.

COSTS OF CHLAMYDIA SCREENING PROGRAMME



*24% of women and 8% of men screened, median 0.4 partners notified per index case
†0.8 partners notified per index case
‡24% of men screened

Main results

In 2008–9 screening was estimated to cost about £46.3m in total and £506 per infection treated. Provision for partner notification within the screening programme cost between £9 and £27 per index case, excluding treatment and testing. The model results suggest that increasing male screening coverage from the baseline value of 8% to 24% (to match female coverage) would cost an extra £22.9m and increase the cost per infection treated to £528, whereas increasing partner notification efficacy from the baseline 0.4 partners per index case to 0.8 would cost an extra £3.3m (nearly £20m less) and would reduce the cost per infection diagnosed to £449 (figure). Increasing screening coverage to 24% in men would cost over six times as much as increasing partner notification to 0.8 but only treat twice as many additional infections.

Results of sensitivity analysis

The user friendly spreadsheet tool (freely available on bmj.com) can be easily modified to explore additional parameter values for other countries or local coordinators.

Limitations

It is not possible to estimate long term cost effectiveness within this model framework, which would require a transmission dynamic model. The definition and measurement of partner notification outcomes of partner notification was identified as a key difficulty for services, with confusion over definition of partner notification outcome measures and denominator populations. The cost perspective taken was that of the NHS and was restricted to consideration of the costs of screening and partner notification, and excluded patient costs, the costs of reinfection, or the cost of complications arising from the initial infection.

Study funding/potential competing interests

Bristol Sexual Health Centre Capacity Building Research Fund supported this study by a grant and by consultancy fees to KT, AG, and EA. KT is supported by an NIHR PDF fellowship. KT and GB also received funding from the NIHR Health Technology Assessment programme. JC, PH, and JM are members of the National Chlamydia Screening Advisory Group and receive expenses payments for this work. EA and AG have done consultancy work for the National Chlamydia Screening Programme. KT and EA were employed by the Health Protection Agency for work on chlamydia screening. PH collaborated in evaluation of a diagnostic test for chlamydia and gonorrhoea by Siemens Healthcare Diagnostics.