Author's response to reviews

Title: Fungal infection-related mortality versus total mortality as an outcome in trials of antifungal agents

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Author's response to reviews: see over
Authors’ response to the peer reviewers’ comments are given below in italics.
23 March 2006

Reviewer's report
Disease specific mortality versus total mortality as outcome in trials of Title: antifungal agents
Version: 1 Date: 18 November 2005
Reviewer: Eric J. J Bow
Reviewer's report:
General
Title: Disease specific mortality versus total mortality as outcome in trials of antifungal agents
Author(s): Due AK, G?tzsche PC, Johansen HK.
Journal: BMC Medical Research Methodology
ID#: 1300953212845187
1.0 Is the question posed by the authors new and well defined?
1.1 Due and colleagues have submitted a systematic review of the literature with a meta-analysis examining the value of fungal infection-related death (FRD) as an acceptable bias-free outcome. The central premise of the submission is that the failure to demonstrate a treatment effect for the outcome of non-fungal infection-related death (NFRD) indicates lack of bias in classification of cause of death as due to or not due to the fungal infection. The authors have selected prophylaxis trials for this evaluation. The value of FRD as an outcome has implications broader that for prophylaxis studies. Does the principle examined herein apply to other life-threatening circumstances in which anti-fungal therapy is administered such as directed therapy for proven/probable(1) invasive fungal infection, or for empirical anti-fungal therapy in persistently febrile neutropaenic patients?

We did not only include all prophylaxis studies but also all empirical studies (and a few treatment studies). We have changed the wording to make this more clear: “prophylactic or empirical treatment”. There is no good reason why our findings should not apply more generally, to all three types of studies, as the same biases are operating and as it is difficult to verify without doubt a suspicion of fungal infection before treatment is instituted. The traditional division between the three types of studies is therefore not sharp and it is prone to a considerable observer variation and variation in definitions and methods between studies. Furthermore, we estimated the outcome as a relative risk, which, in contrast to the risk difference, is rather stable over varying baseline risks for fungal infection.

2.0 Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
2.1 The tool offered for detection of the bias is the relative risk of NFRD as estimated from the total mortality minus the FRD reported in the included trials used as the denominator in the risk calculation (#events / # at risk) divided by the result of the subtraction of FRD from the total number of randomized patients, a term that encompasses both survivors and NFRD. 
2.2 It is not clear to this reviewer, despite the explanation in the text, how this denominator, exclusive of a significant proportion of randomized patients, is representative of the number of patients at risk of NFRD and, more importantly, how this modification of the risk calculation excludes bias in the assignment of the cause of death. By standard estimates, the relative risk (RR) of NFRD would be 0.97, 95%CI 0.82 to 1.14, very similar to the RR of 0.95, 95%CI 0.82 to 1.09 reported in the manuscript. While the authors argue (page 4, paragraph 3, line 2) that the proportion of NFRD should be similar between groups after the subtraction operation provide the groups are comparable, no data are provided to support this assumption. This section of the methods section is
critical to the understanding of the manuscript and acceptance of the conclusions. The description of the estimate for the “at risk” population needs revision, at least in this reviewer’s eyes.

*We cannot perform the analysis the reviewer suggests without having access to individual patient data, which we don’t have and very likely cannot get (e.g. many of the trials are rather old). However, we believe it is not necessary either. We have described in the Discussion that our result is the opposite of what one would expect (a RR below 1.00 is not expected, since, even in the absence of any misclassification bias, more severely ill patients would be expected to survive in the experimental group which should then increase their risk of death, compared with surviving patients in the control group). Because of this result, we believe it is not important how representative the surviving patients are.*

2.3 Neutropaenic cancer patients are subject to multiple diverse mortality risks that include the underlying cancer, drug-related adverse events, pre-existing co-morbidity, and a spectrum of fungal and non-fungal infections. The spectrum of diagnostic robustness of invasive fungal infection (IFI)(1) is directly related to mortality(2). Patients classified as having proven IFI have higher mortalities than those classified as possible IFI. Is it possible that patients with possible IFI who die in the context of a clinical trial of empirical therapy would have their deaths classified as NFRD? These considerations beg the question, is the RR NFRD (and FRD) sensitive to the classification of the IFI?

*That is extremely unlikely since we found a rather large effect of antifungal agents on fungal mortality: 0.57 (95% CI 0.44-0.74) despite the fact that most of the trials were of prophylaxis where the diagnostic uncertainty is greatest.*

2.4 Assignment of cause of death by the investigator is, as the authors suggest, an important source of bias. Unless blinded, the investigator’s knowledge of treatment assignment may also influence assignment of cause of death. Accordingly, an analysis of the trials with regard to blinding of treatment assignment would make the overall analysis more robust. The conclusions reached by the authors may only be valid in the context of blinded trials. This consideration begs the question, is the RR NFRD sensitive to the quality of the study in general and blinding specifically?

*That is a good point. Subgroup analyses should generally be discouraged when the null hypothesis could not be rejected, as was the case in our study. However, we have now done an exploratory analysis which we describe in the Discussion. We included only those trials that were not blinded. The total number of deaths among those who survived the fungal infection was 255, as compared with 649 for the corresponding analysis for all the trials. The relative mortality risk among those who did not die from fungal infection was 0.90 (95% CI 0.72-1.14), which is similar to our estimate of 0.95 (95% CI 0.82-1.09) for all the trials.*

2.5 The trials included in the analyses compare experimental arms with untreated/placebo controls and to active controls. The experimental arms employed agents with variable activities against yeasts and moulds, which in turn have differing mortality risks. Similarly, the active control arms employed agents with differential activities against yeasts and moulds. A study arm, experimental or control, containing fluconazole may have a greater mortality risk for moulds than yeasts than an arm containing a polyene such as amphotericin B. The reader cannot e sure that these factors did not bias against detecting a treatment effect in the RR for FRD or for NFRD. Perhaps further sensitivity analyses examining these outcomes by broad classification of pathogen (yeast versus mould) and by expected spectrum of the experimental agent and active control agent against yeasts and moulds
could provide further insight.

We cannot separate the aetiologies as we do not have access to individual patient data. However, we believe this is not relevant for the type of methodologic study we have done, since, if there had been bias in classification of cause of death, we would have expected this to occur in any type of trial.

2.6 Another bias that affects mortality risk is that of the underlying disease diagnosis (for example, acute leukaemia versus solid tissue malignancy versus lymphoma) and treatment (for example, chemotherapy versus haematopoietic stem cell transplant, allogeneic versus autologous). Maldistributions of these variables may alter the IFI risk as well as the FRD risks and NFRD risks and thus the assignment of cause of death. Would it not be helpful to consider the influence of such biases in the assessment of FRD as an outcome free of bias?

We used RR which is rather robust to such possible differences. Furthermore, since we included only randomised trials, one would not expect a skewed distribution of baseline characteristics over a large number of trials.

2.7 It is unclear why a more conservative analysis based upon a random effects model was not also presented given the heterogeneity (this is not to be confused with the parameters estimated with I²) in designs of studies included in the overall analyses.

There is so little heterogeneity in our three overall estimates (I squares of zero, zero and 6%), that there is no need to use a random effects model (as it gives virtually the same results as a fixed effect model under these circumstances).

3.0 Are the data sound and well controlled?
3.1 The data are derived from randomized, controlled clinical trials. By definition the data are controlled. The question of whether the analyses support the hypothesis that FRD is a bias-free end-point for clinical trials is less certain given the perceived lack of precision for estimating the presence of different types of bias.

We do not agree with this comment. We have written in the Discussion that the confidence interval for our risk estimate, 0.82-1.09, is compatible with the possible existence of minor bias. But it is really a minor bias we are taking about, and our study therefore had quite good power for concluding that “it seems to be reliable to use fungal mortality as the primary outcome in trials of antifungal agents”. Furthermore, we are very cautious as we also say: “Data on total mortality should be reported as well, however, to guard against the possible introduction of harmful treatments as we cannot know whether our findings will apply to future antifungal agents.”

4.0 Does the manuscript adhere to the relevant standards for reporting and data deposition?
4.1 The methodologies for this systematic review were reported in the previously published meta-analyses (references 4, 9-11). The major inclusion criterion for analysis was the reporting of mortality. This is appropriate.

5.0 Are the discussion and conclusions well balanced and adequately supported by the data?
5.1 The discussion is very short and would be in keeping with categories of other publications such as a letter or concise report. The accompanying forest plot figures support the meta-analysis but do not add a great deal to the central thesis of the submission. Figure 1 (a and b) was not helpful in reducing the confusion surrounding the value of (NFRM/(Total N – FRD)) as a tool to judge the presence of bias in assignment of FRD.
We agree that the basic concept was a bit difficult to follow and we have therefore now added additional explanations to the figure so that it can be understood without having to look at the main text.

5.2 Figure 2 supports an overall treatment effect in the pooled weighted analysis for all-cause mortality. There is no discussion of this important observation. The I² score for the relatively robust studies in “02” is high (50.1%) compared to the other analyses in the figure. Why is this so?

The reviewer refers here to five trials that compared fluconazole with no treatment. This is only one of the 10 comparisons we have made in this figure and therefore a subgroup result that is not important for the aim of our study. The heterogeneity is caused by one trial, and with so many included trials and subgroup analyses it is only to be expected that there will be one or a few outliers. There are other problems with some of the trials, e.g. many of them are small and could represent publication bias, and one therefore needs to interpret an effect on overall mortality very cautiously. It is not the focus of this paper to discuss such a possible effect for some of the drugs; we have dealt with this in the reviews we have published on antifungal agents.

6.0 Do the title and abstract accurately convey what has been found?

6.1 The title “Disease specific mortality versus total mortality as outcome in trials of antifungal agents” seems somewhat broad given the focus upon “fungal infection-related mortality” in clinical trials of anti-fungal prophylaxis in neutropaenic cancer patients. The authors might consider modifying the title accordingly. Furthermore, there should be a hyphen between “Disease” and “specific”, and “outcome” should be preceded by “an”.

We agree and have changed the title (and also the text in several places) as suggested.

6.2 The second author’s name appears to be misspelled. Is “G?tzche” not “G?tzsche”?

Thanks for spotting this.

6.3 The abstract is an accurate representation of the text of the manuscript. The conclusion that “fungal mortality” is “safe” for use as a primary outcome is confusing, however. The central premise of the submission is that the failure to demonstrate a treatment effect for the outcome of non-fungal infection-related mortality indicates lack of bias in classification of cause of death as due to or not due to the fungal infection. The authors have selected prophylaxis trials for this evaluation.

We have changed the wording to: “We conclude that it seems to be reliable to use fungal mortality as the primary outcome in trials of antifungal agents”. It is not correct that we only included prophylaxis trials, see above.

7.0 Is the writing acceptable?
7.1 The style and grammatical constructs are acceptable.

8.0 Confidential Comments to the Editors

8.1 Reviewer’s Report. There are several flaws in this submission that make it difficult to accept the conclusions. The most important flaw is the underlying premise of bias in classification of deaths as FRD. Moreover, the structuring of the tool used to estimate bias leave questions of how validity of the variable representing the patients at risk. This manuscript would be acceptable for publication with major compulsory revisions (vide supra). The data contained herein is a useful extension of
work already published.

See above. We do not agree with the reviewer that there should be flaws in our analyses and the reviewer has not guided us as to what else we could have done, considering the aim of our study.

8.2 What Next? Re-review after response to major compulsory revisions.
8.3 Level of Interest. This article is of interest to other meta-analysts who may e contemplating using disease-specific mortality as a primary or secondary outcome.
8.4 Quality of Written English. The revised manuscript will require minimal modifications.
8.5 Statistical Review. Given the methodological nature and this reviewer’s confusion about the assumptions used, a statistical review would be prudent to resolve the issues.

One of us is an experienced meta-analyst, and as there very little in the review that is of a statistical nature (and nothing we are not familiar with), we do not see the rationale for this recommendation. We also note that the second reviewer did not feel a statistical review is necessary but will leave it to the editors to decide.

8.6 Declaration of Competing Interests. The reviewer has no competing interests with regard to this manuscript submission.

References
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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)
Unable to decide on acceptance or rejection until the authors have What next?: responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: Yes
Reviewer's report
Disease specific mortality versus total mortality as outcome in trials of Title: antifungal agents
Version: 1 Date: 16 February 2006
Reviewer: Geoffrey Playford
Reviewer's report:
General
Thanks for the opportunity to review this manuscript. The research question is important, relevant and well defined. In the absence of objective and standardised diagnostic criteria, the method adopted, i.e. assessing whether the proportion of patients not dying from fungal infections but who died from another cause was different in the experimental and control arms of the trials, represents a reasonable approach to this question. However, the limitations of this approach have not been acknowledged in the manuscript. Misclassification of death from either a fungal infection or from another cause may occur in either direction and furthermore may be differential or nondifferential. Thus any misclassification may bias the results either towards or away from null. The potential problems of pooling trials where the direction of misclassification is unpredictable should be acknowledged.

Although the reviewer is correct, in principle, there is a wealth of literature on bias in drug trials that shows that this bias very consistently favours drugs over no treatment, or new drugs over control drugs, also when the issue is classification of outcomes, including death. The recent scandal with the Cox-2-inhibitors illustrates this: A meta-analysis supported by Merck concluded in 2001 that there was no increased risk of arterial thrombosis with the company’s drug, rofecoxib (1), but a meta-analysis not supported by industry (2) showed an increased risk, which was apparent in publications available to the authors of the industry-supported meta-analysis. Rofecoxib was withdrawn because of thromboses in 2004. We made sure that a bias in favour of a new drug would always give an RR in the same direction (see our graphs), and it is for this reason that we made it clear that: “In all trials that compared two drugs, it was easy to decide which was the experimental one and which was the control drug.”


Therefore, we fail to see that it should be a potential problem of pooling trials that the direction of misclassification is unpredictable. It is not particularly unpredictable what happens when the pharmaceutical industry is involved, and it is well documented that clinical investigators have very little influence on data analysis and interpretation of data in industry-sponsored trials:


Further exploration of results could be achieved by sensitivity/subgroup analyses based on possible explanatory variables such as study methodological quality, particularly whether the trial was blinded and especially whether the outcome assessors were blinded to treatment allocation.

It has been demonstrated in several studies that it is not important for meta-analyses whether or not data extractors are blinded, see, for example, Cochrane Handbook for Systematic Reviews of Interventions, available from www.cochrane.org.

See our comment to reviewer 1 above (under 2.4); we have now added a subgroup analysis.

Other subgroup analyses could include time of study or strictness of diagnostic criteria. The manuscript is succinct. The additional figures are important for the manuscript and should be included.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1. Second paragraph of Methods "Provided the two groups are still comparable ..., the proportion of those who died from another cause than fungal infection would be expected to be the same in the two groups". I would have thought that the proportion in such a setting would just as likely be reduced (assuming that at least some of those who have been saved from a fungal death in the experimental arm do not die from another cause) as to stay the same.

Most people (75% in our studies) died from other causes than fungal infections. Those who were treated successfully with an antifungal agent were therefore still at a high risk of death, and we believe that there is no good reason to think that these patients would now have a lower risk of death than those in the control group who survived a fungal infection.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)
1. Acknowledge the potential limitation of the methodology used to address the research questions.
2. Consider sensitivity/subgroup analyses

What next?: Accept after discretionary revisions
Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable
Statistical review: No
Declaration of competing interests: I declare that I have no competing interests