Reviewer's report

Title: Disease specific mortality versus total mortality as outcome in trials of antifungal agents

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Reviewer: Eric J. J Bow

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General

Title: Disease specific mortality versus total mortality as outcome in trials of antifungal agents
Author(s): Due AK, G?tzsche PC, Johansen HK.
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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?

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.
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?

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?

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.

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?

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.

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.

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.

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?

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”.

6.2 Do the second author’s name appears to be misspelled. Is “Gtzche” not “Gtzsche”?

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.

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

References


Respectfully submitted,

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

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

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

**Declaration of competing interests:**

I declare that I have no competing interests.