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Clinical Studies

Mould-active compared with fluconazole prophylaxis to prevent invasive fungal diseases in cancer patients receiving chemotherapy or haematopoietic stem-cell transplantation: a systematic review and meta-analysis of randomised controlled trials

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BACKGROUND: Objectives were to compare systemic mould-active *vs* fluconazole prophylaxis in cancer patients receiving chemotherapy or haematopoietic stem cell transplantation (HSCT).

METHODS: We searched OVID MEDLINE and the Cochrane Central Register of Controlled Trials (1948-August 2011) and EMBASE (1980-August 2011). Randomised controlled trials of mould-active *vs* fluconazole prophylaxis in cancer or HSCT patients were included. Primary outcome was proven/probable invasive fungal infections (IFI). Analysis was completed by computing relative risks (RRs) using a random-effects model and Mantel–Haenszel method.

RESULTS: From 984 reviewed articles, 20 were included in this review. Mould-active compared with fluconazole prophylaxis significantly reduced the number of proven/probable IFI (RR 0.71, 95% CI 0.52 to 0.98; $P = 0.03$). Mould-active prophylaxis also decreased the risk of invasive aspergillosis (IA; RR 0.53, 95% confidence interval (CI) 0.37–0.75; $P = 0.0004$) and IFI-related mortality (RR 0.67, 95% CI 0.47–0.96; $P = 0.03$) but is also associated with an increased risk of adverse events (AEs) leading to antifungal discontinuation (RR 1.95, 95% CI 1.24–3.07; $P = 0.004$). There was no decrease in overall mortality (RR 1.0; 95% CI 0.88–1.13; $P = 0.96$).

CONCLUSION: Mould-active compared with fluconazole prophylaxis significantly reduces proven/probable IFI, IA, and IFI-related mortality in cancer patients receiving chemotherapy or HSCT, but increases AE and does not affect overall mortality. (PROSPERO Registration: CRD42011174)

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Cancer patients receiving intensive chemotherapy or undergoing haematopoietic stem cell transplantation (HSCT) are at an increased risk of invasive fungal infections (IFI); both yeasts and moulds contribute to IFI in these populations (Mahfouz and Anaissie, 2003). IFI are associated with considerable morbidity and mortality. Although invasive aspergillosis (IA) has decreased in recent years (Pagano *et al*, 2010), mortality remains unacceptably high. As a result, emphasis has been placed on prevention of IFI using prophylactic strategies.

Choices for systemic antifungal prophylaxis include fluconazole and agents with activity against moulds. Fluconazole is inexpensive and in general, well tolerated. However, it lacks activity against moulds, in particular against *Aspergillus* spp. In contrast, newer broad-spectrum azoles such as voriconazole and posaconazole, echinocandins such as caspofungin and micafungin, and amphotericin have coverage that extends to yeasts and moulds. However, each of these agents may have specific downsides including toxicity, potential for drug interactions and considerable costs.

Previous randomised trials have shown the benefits of fluconazole prophylaxis when compared with placebo in patients receiving chemotherapy and undergoing HSCT (Goodman *et al*, 1992; Slavin *et al*, 1995; Rotstein *et al*, 1999). However, individual trials comparing mould-active prophylaxis to fluconazole have yielded inconsistent results with most studies failing to show a reduction in proven or probable IFI (Wingard *et al*, 2010). Consequently, there are conflicting recommendations for antifungal prophylaxis from published guidelines (Cornely *et al*, 2009; Freifeld *et al*, 2011), which has led to variability in clinical practice (Lehrnbecher *et al*, 2009).

Although there are many randomised trials which assessed the efficacy of antifungal prophylaxis, most were underpowered to detect a significant difference in the incidence of proven or probable IFI or all-cause mortality. We hypothesised that

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including all available studies that compared mould-active *vs* fluconazole prophylaxis would improve the ability to determine whether mould-active agents are associated with fewer proven or probable IFI and whether these agents are associated with a survival benefit. The primary objective of this review was to determine whether mould-active prophylaxis reduces the incidence of proven or probable IFI, when compared with fluconazole. The secondary objectives were to determine whether mould-active prophylactic strategies, when compared with fluconazole, are associated with a reduction in: (1) incidence of IA; (2) adverse events (AE) requiring discontinuation or modification of antifungal prophylaxis; (3) number of IFI- and IA-related deaths; and (4) all-cause mortality.

METHODS

The reporting of this meta-analysis follows the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Moher *et al*, 2009). Methods of the analysis and inclusion criteria were specified in advance and registered in the PROSPERO registry of systematic reviews (Ethier, 2011).

Eligibility criteria

Randomised controlled trials comparing systemic mould-active to fluconazole prophylaxis were eligible. Any of the following mould-active agents were included as long as they were administered systemically: amphotericin B (conventional and lipid formulations), caspofungin, micafungin, anidulafungin, posaconazole, itraconazole, voriconazole, or ketoconazole. Inclusion criteria were: (1) randomisation between systemic mould-active and fluconazole prophylaxis; and (2) patients of any age receiving chemotherapy for cancer or undergoing HSCT. We excluded (1) studies in which more than one systemic prophylactic anti-fungal agent was given in one of the study arms; (2) studies that did not report any of the primary or secondary outcomes; and (3) studies of pre-emptive or empiric therapy or anti-fungal treatment. There were no restrictions by language or by publication status.

Information sources and search details

We performed an electronic search of OVID MEDLINE (from 1948 to August 2011), EMBASE (from 1980 to August 2011), and The Cochrane Central Register of Controlled Trials (CENTRAL; until the third quarter of 2011). Searches were last updated 24 August 2011. We also reviewed the reference lists of relevant articles and reviews as well as trials registered on the ClinicalTrials.gov website. We searched for conference proceedings from 2005 to 2011 using the Web of Science (version 4.10) as well as abstracts presented within the last 2 years at annual meetings of the American Society of Hematology and American Society of Clinical Oncology.

We used the following search terms in both indexed and text word forms to search all databases: fluconazole, *Aspergillus* or mycoses, prevention or prophylaxis, neoplasm or SCT or neutropenia, with appropriate limits to identify randomised controlled trials (Appendix Table A1 for full search strategy). Two reviewers (MCE and MS) assessed the title and abstract of each reference identified by the search and applied the eligibility criteria. For potentially relevant articles, the full article was obtained and assessed by both authors independently. Final inclusion of studies in the meta-analysis was determined by agreement of both reviewers. If consensus could not be reached, disagreements were resolved by a third study author (LS). Agreement between reviewers was evaluated by using the kappa statistic.

Outcomes

The primary outcome was proven or probable IFI. IFI were re-classified using the revised EORTC/MSG criteria when sufficient data were available and authors used other definitions (De Pauw *et al*, 2008). When re-classification was not possible, the study was not included in the analysis of this outcome. A secondary outcome was IA that was defined as culture-proven *Aspergillus* or *Aspergillus* diagnosed by microscopic examination (De Pauw *et al*, 2008). The time period for IFI and IA observation was during the study period, which varied across studies. Other secondary outcomes were IFI- and IA-related mortality, all-cause mortality and adverse events leading to discontinuation or modification of study drug. The time period for observation of mortality was 3 months. We did not examine possible IFI as there was considerable inconsistency as to how this outcome was defined.

Data collection process

Two reviewers (MCE and MS) independently abstracted data from included trials using a standardised data collection form. Disagreements were resolved by discussion between the two reviewers; if no agreement could be reached, it was pre-specified that a third author (LS) would arbitrate. Corresponding authors were contacted to retrieve additional data if needed.

The following information was extracted: (1) study characteristics (recruitment period, number of subjects, follow-up period, country where study performed, whether study was multicenter, concurrent antibiotic prophylaxis, definitions for IFI, criteria for starting and stopping prophylaxis); (2) characteristics of trial participants (population, diagnosis, age, gender); (3) intervention and comparison (name of drug, dose, route, duration, frequency); and (4) outcomes.

Risk of bias in individual studies

To assess the risk of bias, included articles were examined by two reviewers (MCE and MS) for: (1) generation of sequence allocation; (2) allocation concealment; (3) blinding; (4) incomplete outcome data; and (5) intention-to-treat (ITT) analysis. Definitions/criteria of these items were derived from the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2009).

Statistical analysis

The meta-analysis was performed by computing relative risks (RRs) using a random-effects model as heterogeneity between trials was expected. We followed the ITT principle when we calculated summary RRs with 95% confidence intervals (CI). The Mantel–Haenszel method was chosen as the event rates were relatively low across all outcomes. We considered P-values < 0.05 statistically significant. Synthesis was performed using Review Manager (Version 5.1, The Cochrane Collaboration, 2011, http://ims.cochrane.org/revman/download). Meta-regression also was performed in addition to stratified analyses using SAS-PC software (version 9.2; SAS Institute, Cary, NC, USA).

Sub-group analyses defined *a priori* were performed to investigate the effects of age (children *vs* adults), study population (HSCT *vs* chemotherapy), drug used in the experimental comparison group (amphotericin *vs* mould-active azoles *vs* echinocandins), and dose of fluconazole ($\geqslant 400$ mg per day *vs* < 400 mg per day). We excluded studies that included both chemotherapy and HSCT patients from the study population sub-group analysis. We also examined subgroups by blinding and ITT analysis. Outcomes identified for sub-group analyses were proven/probable IFI, IA, IFI-, and IA-related mortality, overall mortality and AEs requiring antifungal treatment discontinuation or modification.

Concern has been raised about the effectiveness of itraconazole capsule to prevent IFD (Prentice *et al*, 2006) and at least two sets of guidelines have recommended against its use as prophylaxis (Walsh *et al*, 2008; Maertens *et al*, 2011). Consequently, we also conducted a sensitivity analysis excluding the two studies that used itraconazole capsules. There also has been concerns about whether doses of itraconazole solution <400 mg per day is effective (Glasmacher *et al*, 2003) and consequently, we conducted a second sensitivity analysis in which we deleted studies that used doses lower than this threshold amount.

Heterogeneity was initially inspected graphically (forest plot) and assessed statistically using the I^2 statistic and by performing a test for heterogeneity.

We assessed the possibility of publication bias by examining funnel plots for asymmetry (Sutton *et al*, 2000).

RESULTS

A total of 984 titles and abstracts were reviewed (Figure 1); 20 were retrieved for detailed evaluation (Bodey *et al*, 1994; Annaloro *et al*, 1995; Morgenstern *et al*, 1999a; Huijgens *et al*, 1999b; Timmers *et al*, 2000b; Wolff *et al*, 2000b; Koh *et al*, 2002a; Glasmacher *et al*, 2003; Winston *et al*, 2003; Marr *et al*, 2004; van Burik *et al*, 2004; Choi *et al*, 2005; Oren *et al*, 2006b; Cornely *et al*, 2007; Ito *et al*, 2007b; Ullmann *et al*, 2007; Hiramatsu *et al*, 2008b; Sawada *et al*, 2009a; Ota *et al*, 2010; Wingard *et al*, 2010) and all 20 (19 full-text articles and one conference abstract (Ota *et al*, 2010)) satisfied eligibility criteria and were included in the final meta-analysis. The kappa statistic for study inclusion was 1.0, reflecting perfect agreement.

Demographics of the 20 included studies are presented in Table 1. A total of 5725 patients were included in this review with ages ranging from 0.6 to 82 years. Trials were performed in Asia ($n=7$), Europe ($n=5$), North America ($n=5$), and internationally ($n=3$). Half of the studies were multi-centred (10 out of 20, 50.0%). The patient populations were HSCT ($n=14$) and chemotherapy ($n=6$). Children were included in four trials but only one trial comprised of children only. Antibiotic prophylaxis was recommended in 8 out of 20 (40%) of trials. Study regimens included amphotericin B formulations ($n=4$), micafungin ($n=3$), posaconazole ($n=2$), voriconazole ($n=1$), and itraconazole ($n=10$). All studies of echinocandins consisted of micafungin. Fungal prophylaxis was started either with the initiation of chemotherapy ($n=18$) or at the onset of neutropenia ($n=1$; Sawada *et al*, 2009a), and was not available for one study (Choi *et al*, 2005). Routine galatomannan testing was performed in two trials and serum beta-D-glucan testing in one trial (Ito *et al*, 2007a; Ullmann *et al*, 2007; Wingard *et al*, 2010).

Risk of bias assessment is presented in Table 2. The majority of studies did not provide adequate information on sequence allocation and allocation concealment. Only 4 out of 20 (20%) of the studies were blinded and 6 out of 20 (30%) performed an ITT analysis.

The analysis of the primary outcome, which was proven or probable IFI, encompassed 2385 (mould-active group) and 2417 (fluconazole group) patients, in 18 studies. When data from all 18 studies that reported on our primary outcome were pooled, mould-active compared with fluconazole prophylaxis significantly reduced the risk of IFI (RR 0.71, 95% CI 0.52–0.98; $P=0.03$), with moderate heterogeneity ($I^2=$ 33%, $P=0.11$) as illustrated in Table 3 and Figure 2.

Mould-active prophylaxis, when compared with fluconazole prophylaxis, decreased the risk of IA (RR 0.53, 95% CI 0.37–0.75) and IFI-related mortality (RR 0.67, 95% CI 0.47–0.96). However, mould-active prophylaxis was significantly associated with more adverse events leading to antifungal prophylaxis discontinuation or modification when compared with fluconazole prophylaxis (RR 1.95, 95% CI 1.24–3.07). Importantly, mould-active prophylaxis did not significantly influence overall mortality (RR 1.0, 95% CI 0.88–1.13). Funnel plots were reviewed for each of the study outcomes. No apparent asymmetry was seen by visual assessment (data not shown).

The results from the subgroup analyses for 4 of our 5 pre-specified outcomes are presented in Table 4 and Appendix Table A3. Subgroup analysis by age was not possible as only one study included children only. There was no evidence for a difference in the effect of mould-active *vs* fluconazole prophylaxis for any of the outcomes. However, the beneficial effect of mould-active prophylaxis appeared qualitatively greater in studies of other azoles and echinocandins in comparison with amphotericin B formulations. There was no evidence that the effect of mould-active prophylaxis differed by blinding status or application of the ITT principle (Appendix Table A2). The results from the meta-regression are presented in Appendix Table A4 and are consistent with the results from the sub-group analysis.

Appendix Table A5 illustrates the sensitivity analyses that removed the two studies of itraconazole capsule prophylaxis and the three studies that used oral itraconazole solution doses <400 mg per day. The removal of these studies did not impact the results, with the exception of proven or probably IFI which was no longer significant after removing the three studies that used oral itraconazole solution doses <400 mg per day.

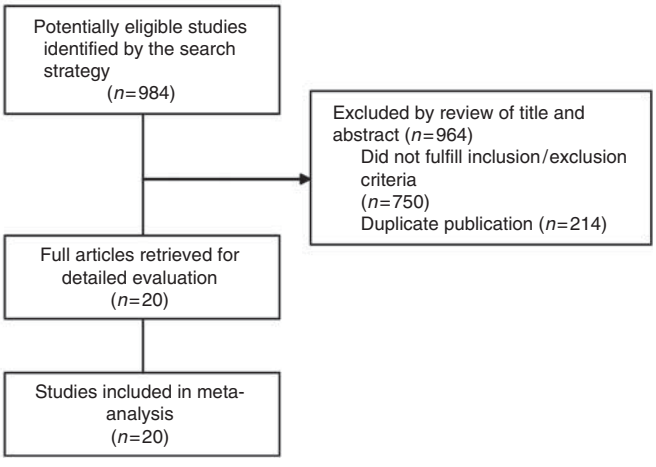

Figure 1 Flow diagram of trial identification and selection.

DISCUSSION

We found that in patients with cancer receiving chemotherapy or HSCT, mould-active prophylaxis when compared with fluconazole prophylaxis was associated with a clinically relevant reduction in proven or probable IFI, IA and IFI-related mortality. However, mould-active prophylaxis was also associated with a significantly increased risk of adverse events requiring discontinuation or modification of therapy and did not affect overall mortality.

These results are in keeping with those from a previous review comparing mould-active to fluconazole prophylaxis that was conducted as a sub-group analysis of a large review; this review included studies published up to 2007 (Robenshtok *et al*, 2007). Similar to our study, that review found that mould-active prophylaxis significantly reduced documented IFI, IA, and IFI-related mortality, and did not impact on all-cause mortality. Our results provide important new information since six new trials comparing fluconazole to systemic mould-active prophylaxis were added (Choi *et al*, 2005; Ito *et al*, 2007a; Hiramatsu *et al*, 2008a; Sawada *et al*, 2009b; Ota *et al*, 2010; Wingard *et al*, 2010), which

Table 1 Characteristics of included trials that compare fluconazole *vs* mould-active antifungal prophylaxis

Study author	Pub year	Multi-centre	*N*	Population	Mould-active dose	Fluconazole dose	Prophylaxis end	Surro-gate testing[a]
Bodey *et al*, 1994	1994	No	77	Hem malignancy	CAB 0.17 mg kg^{-1} per dose IV TID	400 mg per dose PO/IV OD	ANC > 1000 μl^{-1} or 8 weeks	No
Annaloro *et al*, 1995	1995	No	59	HSCT (auto, allo)	Itraconazole 400 mg per dose PO OD	300 mg per dose PO OD	Neutropenia resolution	No
Huijgens *et al*, 1999a	1999	No	202	Hem malignancy, HSCT (auto)	Itraconazole 100 mg per dose PO BID	50 mg per dose PO BID	ANC > 500 μl^{-1}	No
Morgenstern *et al*, 1999b	1999	Yes	581	Hem malignancy, HSCT (auto, allo)	Itraconazole 2.5 mg kg^{-1} per dose PO BID	100 mg per dose PO OD	ANC > 1000 μl^{-1} × 7 days	No
Timmers *et al*, 2000a	2000	No	24	Hem malignancy, HSCT (auto, allo)	Amphotericin B colloidal dispersion 2 mg kg^{-1} per dose IV OD	200 mg per dose PO OD	ANC > 500 μl^{-1}	No
Wolff *et al*, 2000a	2000	Yes	355	HSCT (auto, allo)	CAB 0.2 mg kg^{-1} per dose IV OD	400 mg per dose PO/IV OD	ANC > 500 μl^{-1}	No
Koh *et al*, 2002b	2002	No	186	HSCT (auto, allo)	CAB 0.2 mg kg^{-1} per dose IV OD	200 mg per dose PO OD	ANC > 500 μl^{-1} × 3 days	No
Winston *et al*, 2003	2003	Yes	138	HSCT (allo)	Itraconazole 200 mg per dose IV BID × 4 then 200 mg per dose IV OD × 12 then 200 mg per dose PO BID until D + 100	400 mg per dose IV OD × 14 then 400 mg per dose PO OD until D + 100	D + 100	No
Marr *et al*, 2004	2004	No	299	HSCT (allo)	Itraconazole 2.5 mg kg^{-1} per dose PO TID or 200 mg per dose IV OD	400 mg per dose PO/IV OD	D + 120–180 days	No
van Burik *et al*, 2004	2004	Yes	882	HSCT (auto, allo)	Micafungin 50 mg per dose IV OD	400 mg per dose IV OD	ANC ⩾ 500 μl^{-1} × 5 days or D + 42	No
Choi *et al*, 2005	2005	No	78	HSCT (allo)	Itraconazole 200 mg per dose PO OD	200 mg per dose PO OD	NS	No
Glasmacher *et al*, 2006	2006	Yes	494	Hem malignancy	Itraconazole 5 mg kg^{-1} per dose PO BID	400 mg per dose PO/IV OD	ANC > 1000 μl^{-1} or 8 weeks	No
Oren *et al*, 2006a	2006	No	195	Hem malignancy, HSCT (auto, allo)	Itraconazole 200 mg per dose PO/IV BID	400 mg per dose PO/IV OD	Neutropenia resolution or 8 weeks	No
Comely *et al*, 2007	2007	Yes	544	Hem malignancy	Posaconazole 200 mg per dose PO/IV BID	400 mg per dose PO/IV OD	Neutropenia resolution or 12 weeks	No
Ito *et al*, 2007a	2007	Yes	209	Hem malignancy	Itraconazole 200 mg per dose PO OD	200 mg per dose PO OD	ANC > 1000 μl^{-1} or leukocytes ⩾ 2 μl^{-1}	Yes
Ullmann *et al*, 2007	2007	Yes	600	GVHD	Posaconazole 200 mg per dose PO TID	400 mg per dose PO OD	112 days	Yes
Hiramatsu *et al*, 2008a	2008	No	100	HSCT (auto, allo)	Micafungin 150 mg per dose IV OD	400 mg per dose IV OD	ANC > 500 μl^{-1} × 5 or D + 42	No
Sawada *et al*, 2009b	2009	Yes	107	Hem malignancy, HSCT (allo/auto)	Micafungin 2 mg kd^{-1} per dose IV OD	10 mg kg^{-1} per dose IV OD	ANC > 500 μl^{-1}	No
Ota *et al*, 2010	2010	No	73	HSCT (auto, allo)	Itraconazole 200 mg per dose PO/IV OD	400 mg per dose PO/IV OD	D + 28	No
Wingard *et al*, 2010	2010	Yes	600	HSCT (allo)	Voriconazole 200 mg per dose PO BID	400 mg per dose PO OD	D + 100	Yes

Abbreviations: allo = allogeneic; ANC = absolute neutrophil count; auto = autologous; BID = twice daily; CAB = conventional amphotericin B; D = day of HSCT; GVHD = graft-*vs*-host disease; Hem = haematological; HSCT = haematopoietic stem cell transplantation; IV = intravenous; *N* = total number of subjects randomised; NS = not specified; OD = once daily; Pub = publication; PO = oral; TID = three times daily. [a]Surrogate marker evaluation for invasive fungal infection includes galactomannin and beta-D glucan testing.

Table 2 Risk of bias assessment of included articles

Study author	Adequate sequence generation	Adequate allocation concealment	Blinding	Description of withdrawals and dropouts	Intention to treat analysis	Selective outcome report
Bodey *et al*, 1994	Yes	Unclear	No	Yes	No	No
Annaloro *et al*, 1995	Unclear	Unclear	No	No	Yes	No
Huijgens *et al*, 1999a	Unclear	Unclear	Yes	Yes	No	No
Morgenstern *et al*, 1999b	Yes	Inadequate	No	No	No	Yes
Timmers *et al*, 2000a	Unclear	Unclear	No	No	No	No
Wolff *et al*, 2000a	Unclear	Unclear	No	No	Yes	No
Koh *et al*, 2002b	Unclear	Unclear	No	No	Yes	No
Winston *et al*, 2003	Unclear	Yes	No	Yes	No	No
Marr *et al*, 2004	Unclear	Unclear	No	Yes	No	No
van Burik *et al*, 2004	Yes	Yes	Yes	Yes	No	No
Choi *et al*, 2005	Unclear	Unclear	No	No	No	No
Glasmacher *et al*, 2006	Yes	Yes	No	Yes	No	No
Oren *et al*, 2006a	Yes	Unclear	No	No	No	No
Comely *et al*, 2007	Unclear	Unclear	No	No	Yes	No
Ito *et al*, 2007a	Yes	Unclear	No	Yes	No	No
Ullmann *et al*, 2007	Unclear	Unclear	Yes	No	Yes	No
Hiramatsu *et al*, 2008a	Unclear	Unclear	No	Yes	No	No
Sawada *et al*, 2009b	Unclear	Yes	No	No	No	No
Ota *et al*, 2010	Unclear	Unclear		No	No	No
Wingard *et al*, 2010	Yes	Yes	Yes	Yes	Yes	No

Table 3 Synthesised primary and secondary outcomes of mould-active *vs* fluconazole prophylaxis

Outcome	Trials (patients)	RR (95% CI)[a]	*P*-value
Proven or probable IFI	18 (4802)	0.71 (0.52, 0.98)	0.03
Invasive aspergillosis	15 (4503)	0.53 (0.37, 0.75)	0.0004
Adverse events requiring antifungal treatment discontinuation or modification	16 (4493)	1.95 (1.24, 3.07)	0.004
IFI-related mortality	15 (4272)	0.67 (0.47, 0.96)	0.03
Invasive aspergillosis-related mortality	9 (2614)	0.62 (0.23, 1.71)	0.36
Overall mortality	16 (4870)	1.00 (0.88, 1.13)	0.96

Abbreviations: CI = confidence interval; IFI = invasive fungal infection; RR = risk ratio. [a]RR < 1 represents an advantage of mould-active coverage using a random-effects model.

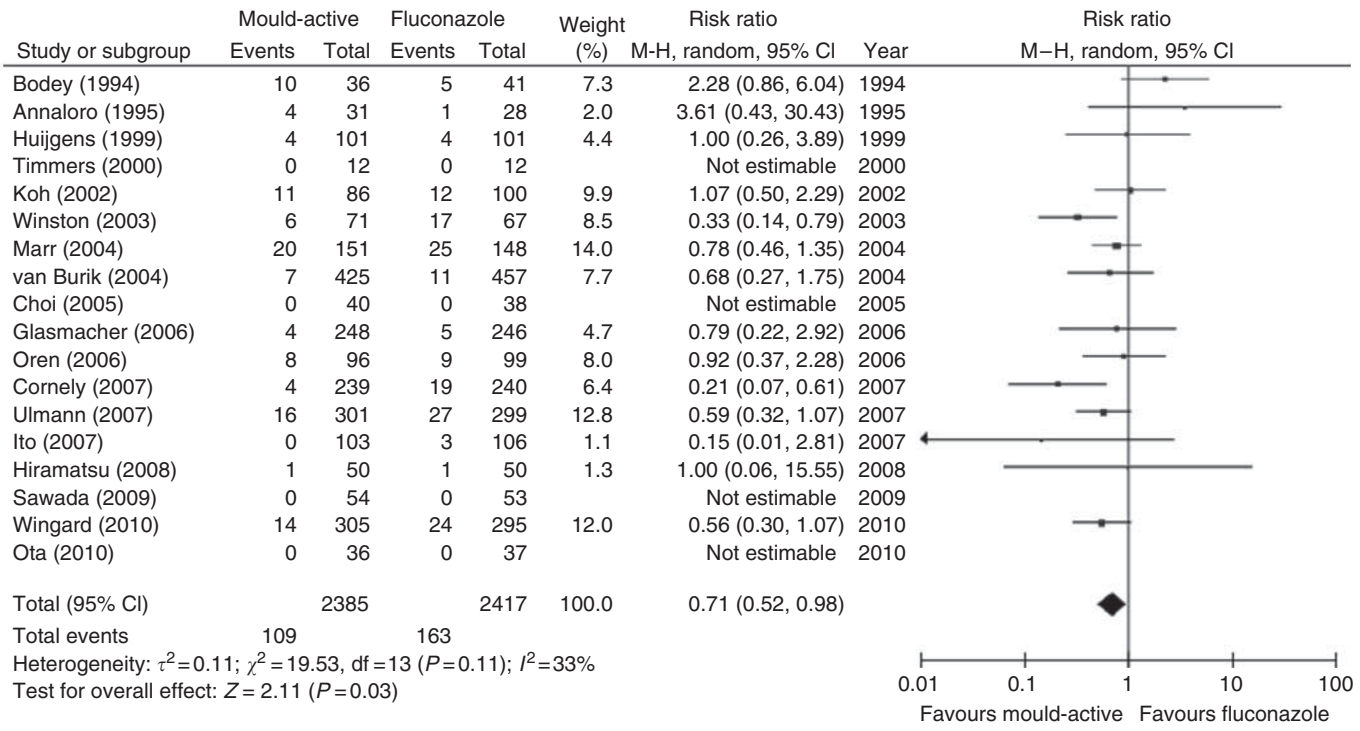

Figure 2 Forest plot of effect of mould-active *vs* fluconazole prophylaxis on the primary outcome, proven or probable invasive fungal infection. Squares to the left of the vertical line indicate a decreased risk of developing an event in patients receiving mould-active prophylaxis. Horizontal lines through the squares represent 95% CIs. The diamonds represents the overall RR from the meta-analyses and the corresponding 95% CIs.

allowed more precise estimation of the effect of mould-active prophylaxis on overall mortality. Furthermore, we examined an additional clinically important outcome, namely adverse events resulting in discontinuation of antifungal prophylaxis, which provides more information to judge the overall utility of mould-active prophylaxis.

We found that mould-active prophylaxis, when compared with fluconazole prophylaxis, reduces IFI-related mortality but does not influence overall mortality with a point estimate RR of 1.0. The 95% CI around the overall mortality estimate does not exclude clinically meaningful benefit or harm since the interval was 0.88–1.13. As IFI-related mortality is a component of overall mortality, it is interesting to see discordance in these two results. There are at least three possibilities to explain this discordance. First, the proportion of IFI-related mortality could be such a small portion of overall mortality that reductions in IFI-related mortality may not detectably impact on mortality. However, there are two observations that argue against this hypothesis. First, the point estimate for overall mortality was 1.0, which suggests no reduction in mortality. Second, mortality was observed for only 3 months and thus, it is hard to envision that IFI-related mortality would be a small proportion of overall mortality within this time frame in these populations. The second possibility that may explain the discrepancy between a reduction in IFD incidence and no effect on overall mortality may relate to the use of galactomannan tests (Marr *et al*, 2005). Mould-active agents are known to reduce the sensitivity of this test and thus, it is possible that the reduction in IFD seen with anti-mould agents is actually spurious. The third possibility is that mould-active prophylaxis increases non-IFI-related deaths. This hypothesis is supported by the increase in adverse events observed in the mould-active prophylaxis arm. Furthermore, it is possible that drug interactions further contributed to increased patient deaths.

There are at least three downsides of mould-active antifungal prophylaxis. First, mould-active prophylaxis may be associated with increased adverse events compared with fluconazole prophylaxis as we have demonstrated. Second, mould-active prophylaxis with non-fluconazole azoles may be associated with significant drug interactions and the impact of these interactions has not been fully evaluated. Third is the issue of costs. Many of the mould-active agents are associated with large costs given the duration of prophylaxis for patients with leukaemia or undergoing allogeneic

Table 4 Stratified analyses by mould-active agent

Outcome	Trials (patients)	RR[a] (95% CI)	*P*-value	*P*-value for interaction test
Mould-active agent				
Proven or probable IFI				0.1
Amphotericin	3 (287)	1.46 (0.70, 3.05)	0.31	
Other azoles	12 (3426)	0.60 (0.43, 0.84)	0.003	
Echinocandin	3 (1089)	0.71 (0.29, 1.73)	0.45	
Invasive aspergillosis				0.29
Amphotericin	3 (618)	1.18 (0.28, 4.97)	0.82	
Other azoles	9 (2796)	0.52 (0.36, 0.76)	0.0006	
Echinocandin	3 (1089)	0.19 (0.03, 1.11)	0.07	
IFI-related mortality				
Amphotericin	4 (642)	0.91 (0.39, 2.16)	0.83	
Other azoles	9 (2648)	0.64 (0.38, 1.08)	0.09	
Echinocandin	2 (982)	0.70 (0.12, 4.28)	0.70	
IA-related mortality				0.43
Amphotericin	2 (101)	3.41 (0.14, 81.07)	0.45	
Other azoles	5 (1531)	0.63 (0.18, 2.13)	0.46	
Echinocandin	2 (982)	0.27 (0.03, 2.38)	0.24	
Overall mortality				0.79
Amphotericin	3 (618)	1.11 (0.78, 1.59)	0.55	
Other azoles	11 (3270)	0.99 (0.86, 1.14)	0.89	
Echinocandin	2 (982)	0.89 (0.42, 1.88)	0.76	
AEs requiring antifungal treatment discontinuation or modification				0.001
Amphotericin	4 (642)	5.98 (1.20, 29.86)	0.03	
Other azoles	10 (2869)	1.92 (1.19, 3.08)	0.007	
Echinocandin	2 (982)	0.59 (0.34, 1.03)	0.06	

Abbreviations: AEs = adverse events; CI = confidence interval; IA = invasive aspergillosis; IFI = invasive fungal infection; RR = risk ratio. [a]RR < 1 represents an advantage of mould-active coverage compared with fluconazole using a random-effects model.

HSCT. Cost-effectiveness analyses have shown that posaconazole is a cost-effective strategy for preventing IFI, compared with fluconazole, in patients with GVHD and with acute myeloid leukaemia/myelodysplastic syndrome (Stam *et al*, 2008; de la Camara *et al*, 2010; Dranitsaris and Khoury, 2011). In adult patients undergoing HSCT, micafungin has been shown to reduce hospital costs and total patient costs (Schonfeld *et al*, 2008) and to be cost effective (Sohn *et al*, 2009), compared with fluconazole. However, these analyses have been based upon single studies rather than synthesised results. Further exploration of costs that take into consideration patient preferences are warranted. Finally, there has been little evaluation of patient preferences for antifungal prophylaxis. Agents such as posaconazole, voriconazole and itraconazole have an oral formulation and thus, may have a lesser impact on quality of life given that administration may occur on an outpatient basis. However, compliance of oral antifungal prophylaxis may be lower (Lehrnbecher *et al*, 2008). In contrast, amphotericin B formulations and echinocandins are only available in parenteral formulation and, thus, their administration in a prophylactic manner would be expected to have a sizeable impact on quality of life.

This study has several limitations. First and most importantly, we combined several different classes of mould-active antifungals that are expected to have different efficacy and toxicity profiles. However, the stratified analysis failed to illustrate important differences in outcome by mould-active antifungal class. Second, fungal classification and reporting was not consistent in the studies included although we attempted to address this limitation by re-classifying infections using the EORTC/MSG definitions for IFI (Ascioglu *et al*, 2002). Third, it is possible that surveillance for IFI using galactomannan and beta-D-glucan testing may have altered the efficacy of mould-active prophylaxis. There are an insufficient number of studies that used such testing to be able to explore this effect. Finally, it is also important to mention that only one study included children only, and thus, we are unable to determine if the effect of mould-active prophylaxis compared with fluconazole differs between children and adults. This deficiency supports the need for future randomised trials in children in order determine the effect of mould-active prophylaxis in paediatrics.

Future studies should attempt to better describe the potential benefits and downsides of mould-active prophylaxis. This may be accomplished through future randomised trials of agents thought to be less toxic and through individual patient-level meta-analyses. Furthermore, patient preferences and costs deserve future exploration. Mould-active antifungal prophylaxis may have a large economic impact on care of patients with haematological malignancy and undergoing HSCT; we must be relatively certain of benefits before routine implementation.

In conclusion, this meta-analysis demonstrates that prophylaxis with mould-active compared with fluconazole prophylaxis significantly reduces the number of proven or probable IFI, IA, and IFI-related mortality in patients receiving chemotherapy or undergoing HSCT. However, mould-active antifungal prophylaxis also increases adverse events leading to antifungal modification or discontinuation and does not impact on overall mortality. Future work to better understand the benefits and downsides of individual classes of mould-active antifungals and to explore patient preferences and costs is warranted.

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APPENDIX

Table A1 Search strategies used to identify randomised study of mould-active *vs* fluconazole antifungal prophylaxis in patients with cancer or undergoing haematopoietic stem cell transplantation

#	Searches	Results
Ovid MEDLINE(R) 1948 to August (week 2) 2011 (run on August 24, 2011)		
1	Fluconazole/ or (fluconazol* or flucolich or arnazole or beagyne or elazor or flucobeta or solacap or diflucan or triflucan or 'uk 49858' or uk49858 or neofomiral or lavisa or zonal or 'fluc hexal' or fluchexal or oxifungol or fungata or loitin or flunazul or zoltrix).mp.	13 405
2	exp Aspergillus/pc or (exp Aspergillus/ and (prophyla* or prevent*).mp.) or exp Mycoses/pc or (exp Mycoses/ and (prophyla* or prevent*).mp.) or (prophylaxis or (prevent* adj2 (fungal or fungus))).ti,ab.	64 991
3	Stem Cell Transplantation.mp. or exp Stem Cell Transplantation/	45 185
4	exp neoplasms/ or (cancer or oncolog*).mp.	2 389 250
5	exp Neutropenia/ or neutropeni*.mp.	28 301
6	3 or 4 or 5	2 426 526
7	1 and 2 and 6	473
8	randomised controlled trial.pt.	314 177
9	controlled clinical trial.pt.	83 186
10	randomised.ab.	220 043
11	drug therapy.fs.	1 486 777
12	randomly.ab.	158 898
13	trial.ab.	227 567
14	groups.ab.	1 054 838
15	8 or 9 or 10 or 11 or 12 or 13 or 14	2 740 074
16	exp animals/ not humans.sh.	3 651 958
17	15 not 16	2 325 347
18	7 and 17	343
Database: EMBASE <1980 to 2011 Week 33> (run on 24 August 2011)		
1	fluconazole/ or (fluconazol* or flucolich or arnazole or beagyne or elazor or flucobeta or solacap or diflucan or triflucan or 'uk 49858' or uk49858 or neofomiral or lavisa or zonal or 'fluc hexal' or fluchexal or oxifungol or fungata or loitin or flunazul or zoltrix or Afungil or Alflucoz or Baten or Biocanol or Biozolene or CCRIS 7211 or Canzol or Cryptal or DRG-0005 or Dimycon or Elazor or Mutum or Pritenzol or Syscan or Triconal or Zemyc or Zoltec).mp.	29 035
2	(exp Aspergillus/ and (prevent* or prophyla*)).mp. or exp mycosis/pc or (exp mycosis/ and (prevent* or prophyla*)).mp. or ((exp Aspergillus/ or exp mycosis/) and (prophylaxis/ or infection prevention/))	16 911
3	stem cell transplantation.mp. or exp stem cell transplantation/	59 342
4	exp neoplasms/ or (cancer or oncolog*).mp.	2 848 209
5	exp NEUTROPENIA/ or exp FEBRILE NEUTROPENIA/ or neutropenia.mp.	61 135
6	3 or 4	2 876 781
7	1 and 2 and 6	1655
8	randomised controlled trial/ or ct.fs. or random$.mp. or doubl$adj blind$.mp.	996 967
9	7 and 8	554
EBM Reviews—Cochrane Central Register of Controlled Trials, 3rd Quarter 2011 (run on 24 August 2011)		
1	fluconazole/ or (fluconazol* or flucolich or arnazole or beagyne or elazor or flucobeta or solacap or diflucan or triflucan or 'uk 49858' or uk49858 or neofomiral or lavisa or zonal or 'fluc hexal' or fluchexal or oxifungol or fungata or loitin or flunazul or zoltrix or Afungil or Alflucoz or Baten or Biocanol or Biozolene or CCRIS 7211 or Canzol or Cryptal or DRG-0005 or Dimycon or Elazor or Mutum or Pritenzol or Syscan or Triconal or Zemyc or Zoltec).mp.	668
2	exp Aspergillus/pc or (exp Aspergillus/ and (prophyla* or prevent*).mp.) or exp Mycoses/pc or (exp Mycoses/ and (prophyla* or prevent*).mp.) or (prophylaxis or (prevent* adj2 (fungal or fungus))).ti,ab.	10 404
3	Stem Cell Transplantation.mp. or exp Stem Cell Transplantation/ or exp Bone Marrow Transplantation/	2679
4	exp neoplasms/ or (cancer or oncolog*).mp.	56 297
5	neutropenia.mp. or exp Neutropenia/	3010
6	3 or 4 or 5	58 299
7	1 and 2 and 6	104

Table A2 Stratified analyses by blinding and intention to treat analysis

Outcome	Trials (patients)	RR* (95% CI)	*P*-value	*P*-value for interaction test
Blinding				
Proven or probable IFI				0.52
Blinded	4 (2284)	0.62 (0.42, 0.91)	0.01	
Not blinded	14 (2518)	0.71 (0.52, 0.98)	0.27	
Invasive aspergillosis				0.60
Blinded	4 (2284)	0.47 (0.23, 0.98)	0.04	
Not blinded	11 (22196)	0.59 (0.37, 0.95)	0.03	

Table A2 *(Continued)*

Outcome	Trials (patients)	RR* (95% CI)	*P*-value	*P*-value for interaction test
IFI-related mortality				0.88
Blinded	3 (1686)	0.68 (0.19, 2.40)	0.54	
Not blinded	12 (2586)	0.75 (0.49, 1.15)	0.19	
IA-related mortality				0.60
Blinded	2 (1084)	0.84 (0.15, 4.91)	0.85	
Not blinded	7 (1530)	0.46 (0.12, 1.77)	0.26	
Overall mortality				0.23
Blinded	4 (2284)	0.92 (0.76, 1.11)	0.36	
Not blinded	12 (2586)	1.07 (0.90, 1.28)	0.44	
ITT analysis				
Proven or probable IFI				0.83
ITT	4 (1445)	0.74 (0.46, 1.17)	0.2	
No ITT	14 (3357)	0.69 (0.44, 1.07)	0.1	
Invasive aspergillosis				0.55
ITT	5 (1800)	0.47 (0.27, 0.80)	0.006	
No ITT	10 (2703)	0.58 (0.37, 0.91)	0.02	
IFI-related mortality				0.60
ITT	5 (1280)	0.60 (0.27, 1.33)	0.21	
No ITT	10 (2992)	0.77 (0.49, 1.22)	0.27	
IA-related mortality				NA
ITT	1 (59)	Not estimable	NA	
No ITT	8 (2555)	0.62 (0.23, 1.71)	0.36	
Overall mortality				NA
ITT	0 (0)	Not estimable	NA	
No ITT	16 (4870)	1.00 (0.88, 1.13)	0.96	

Abbreviations: CI = confidence interval; IA = invasive aspergillosis; IFI = invasive fungal infection; ITT = intention-to-treat; NA = not applicable; RR = relative risk. *RR < 1 represents an advantage of mould-active coverage compared with fluconazole using a random-effects model.

Table A3 Stratified analyses by study population and fluconazole dose

Outcome	Trials (patients)	RR* (95% CI)	*P*-value	*P*-value for interaction test
Study population				
Proven or probable IFI				0.82
HSCT	9 (2415)	0.70 (0.49, 0.99)	0.004	
Chemotherapy	4 (1259)	0.59 (0.15, 2.27)	0.45	
Invasive aspergillosis				0.73
HSCT	8 (2619)	0.47 (0.29, 0.75)	0.002	
Chemotherapy	3 (780)	0.60 (0.16, 2.28)	0.45	
IFI-related mortality				0.96
HSCT	8 (2097)	0.81 (0.50, 1.31)	0.39	
Chemotherapy	2 (571)	0.78 (0.17, 3.46)	0.74	
IA-related mortality				0.23
HSCT	4 (1065)	0.27 (0.03, 2.38)	0.24	
Chemotherapy	2 (571)	1.69 (0.21, 13.59)	0.62	
Overall Mortality				0.42
HSCT	9 (2697)	1.06 (0.90, 1.25)	0.50	
Chemotherapy	2 (571)	0.86 (0.54, 1.38)	0.54	
AEs requiring antifungal treatment discontinuation or modification				0.43
HSCT	8 (2111)	2.14 (0.94, 4.87)	0.07	
Chemotherapy	3 (780)	1.51 (1.16, 1.98)	0.0003	
Fluconazole dose				
Proven or probable IFI				0.18
Fluconazole ⩾400 mg per day	12 (4044)	0.65 (0.46, 0.93)	0.02	
Fluconazole <400 mg per day	6 (758)	1.07 (0.57, 2.00)	0.84	
Invasive aspergillosis				0.11
Fluconazole ⩾400 mg per day	11 (3847)	0.49 (0.34, 0.70)	0.0001	
Fluconazole <400 mg per day	4 (656)	1.42 (0.41, 4.93)	0.59	
IFI-related mortality				0.14
Fluconazole ⩾400 mg per day	9 (3142)	0.57 (0.38, 0.86)	0.007	
Fluconazole <400 mg per day	6 (1130)	1.22 (0.49, 3.02)	0.67	
IA-related mortality				0.87
Fluconazole ⩾400 mg per day	5 (1748)	0.51 (0.13, 1.95)	0.32	
Fluconazole <400 mg per day	4 (866)	0.63 (0.07, 6.09)	0.69	

Table A3 *(Continued)*

Outcome	Trials (patients)	RR* (95% CI)	*P*-value	*P*-value for interaction test
Overall mortality				0.87
Fluconazole ⩾400 mg per day	10 (3740)	0.98 (0.85, 1.12)	0.76	
Fluconazole <400 mg per day	6 (1130)	1.03 (0.57, 1.88)	0.92	
AEs requiring antifungal treatment discontinuation or modification				0.03
Fluconazole ⩾400 mg per day	10 (3213)	1.49 (0.91, 2.43)	0.12	
Fluconazole <400 mg per day	6 (1280)	3.19 (2.01, 5.05)	0.0001	

Abbreviations: AEs = adverse events; CI = confidence interval; HSCT = haematopoietic stem cell transplantation; IA = invasive aspergillosis; IFI = invasive fungal infection; ITT = intention-to-treat; RR = relative risk. *RR < 1 represents an advantage of mould-active coverage compared with fluconazole using a random-effects model.

Table A4 Meta-regression for primary and secondary outcomes of mould-active *vs* fluconazole prophylaxis

Outcome	β	s.e.	*P*-value
Proven or probable IFI			
HSCT	−0.07	0.35	0.831
Amphotericin	0.86	0.36	0.017
Echinocandin	0.19	0.48	0.698
Other azoles	REF	REF	
Fluconazole ⩾400 mg per day	−0.52	0.40	0.190
Blinding	−0.22	0.26	0.403
ITT	−0.24	0.25	0.350
Invasive aspergillosis			
HSCT	−0.35	0.38	0.363
Amphotericin	0.91	0.76	0.233
Echinocandin	−0.90	0.91	0.326
Other azoles	REF	REF	
Fluconazole ⩾400 mg per day	−1.12	0.64	0.080
Blinding	−0.10	0.36	0.780
ITT	−0.38	0.36	0.286
Adverse events requiring antifungal treatment discontinuation or modification			
HSCT	−0.29	0.52	0.584
Amphotericin	1.06	0.67	0.112
Echinocandin	−1.09	0.68	0.112
Other azoles	REF	REF	
Fluconazole ⩾400 mg per day	−0.83	0.48	0.086
Blinding	−1.12	0.30	0.0002
ITT	−0.13	0.59	0.833
IFI-related mortality			
HSCT	−0.10	0.48	0.831
Amphotericin	0.37	0.54	0.495
Echinocandin	0.13	0.98	0.896
Other azoles	REF	REF	
Fluconazole ⩾400 mg per day	−0.70	0.46	0.129
Blinding	−0.34	0.41	0.404
ITT	−0.42	0.39	0.282
Invasive aspergillosis-related mortality			
HSCT	−0.77	1.35	0.569
Amphotericin	1.17	1.40	0.403
Echinocandin	−1.10	1.66	0.506
Other azoles	REF	REF	
Fluconazole ⩾400 mg per day	−0.50	0.97	0.605
Blinding	0.54	1.00	0.590
ITT	0.35	2.06	0.866
Overall mortality			
HSCT	0.10	0.20	0.619
Amphotericin	0.14	0.22	0.510
Echinocandin	−0.16	0.30	0.591
Other azoles	REF	REF	
Fluconazole ⩾400 mg per day	−0.17	0.24	0.47
Blinding	−0.14	0.15	0.341
ITT	−0.05	0.15	0.754

Abbreviations: HSCT = haematopoietic stem cell transplantation; IFI = invasive fungal infection; ITT = intention-to-treat; REF = reference category; s.e. = standard error.

Table A5 Sensitivity analyses for primary and secondary outcomes of mould-active *vs* fluconazole prophylaxis

	Analyses for all included studies		**Sensitivity analysis-studies of itraconazole capsules removed (Annaloro *et al*, 1995; Huijgens *et al*, 1999b)**	
Outcome	**Risk ratio* (95% CI)**	***P*-value**	**Risk ratio* (95% CI)**	***P*-value**
Proven or probable IFI	0.71 (0.52, 0.98)	0.03	0.68 (0.49, 0.94)	0.02
Invasive aspergillosis	0.53 (0.37, 0.75)	0.0004	0.50 (0.35, 0.71)	0.0001
Adverse events requiring antifungal treatment discontinuation or modification	1.95 (1.24, 3.07)	0.004	1.95 (1.24, 3.07)	0.004
IFI-related mortality	0.67 (0.47, 0.96)	0.03	0.62 (0.43, 0.90)	0.01
Invasive aspergillosis-related mortality	0.62 (0.23, 1.71)	0.36	0.41 (0.12, 1.39)	0.15
Overall mortality	1.00 (0.88, 1.13)	0.96	0.99 (0.87, 1.13)	0.85
			Sensitivity analysis-studies of Itraconazole 200 mg per day removed (Choi *et al*, 2005; Ito *et al*, 2007b; Ota *et al*, 2010)	
Proven or probable IFI	0.71 (0.52, 0.98)	0.03	0.72 (0.53, 0.99)	0.05
Invasive aspergillosis	0.53 (0.37, 0.75)	0.0004	0.54 (0.38, 0.76)	0.0005
Adverse events requiring antifungal treatment discontinuation or modification	1.95 (1.24, 3.07)	0.004	1.85 (1.13, 3.03)	0.01
IFI-related mortality	0.67 (0.47, 0.96)	0.03	0.66 (0.46, 0.95)	0.02
Invasive aspergillosis-related mortality	0.62 (0.23, 1.71)	0.36	0.62 (0.23, 1.71)	0.36
Overall mortality	1.00 (0.88, 1.13)	0.96	1.00 (0.88, 1.14)	0.98

Abbreviations: CI = confidence interval; IFI = invasive fungal infection. *RR < 1 represents an advantage of mould-active coverage compared with fluconazole using a random-effects model.