

The Efficacy and Safety of Prophylactic Fluconazole Prevent Invasive Fungal Infection in Preterm Very Low Birth Weight Infants: An Update Meta-analysis

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Abstract

Objective: To evaluate the efficacy and safety of prophylactic use of fluconazole in VLBW infants.

Methods: We searched electronic databases from inception through December 2017. We included RCTs that compared the efficacy of prophylactic fluconazole on IFI versus placebo in VLBW infants.

Results: We identified 8 eligible trials that enrolled 1392 infants. There was significant effect of prophylactic fluconazole on fungal colonization (RR, 0.31, 95%CI:-0.24 to 0.41; P<0.00001). Effect of prophylactic fluconazole on IFI in VLBW infants: RR: 0.42(95%CI 0.23 to 0.76; P=0.004). However, prophylactic fluconazole did not reduce mortality in VLBW infants (RR 0.76, 95% CI 0.58 to 1.01; P = 0.06). Studies did not report significant adverse reactions.

Conclusion: This updated meta-analysis showed that the incidences of fungal colonization and IFI in VLBW infants were significantly reduced by prophylactic fluconazole. Further studies should focus on morbidity, mortality and long term neurodevelopmental outcomes with adequately powered.

Keywords: Fluconazole; Prophylactic; Very Low Birth Weight; Efficacy; Safety; Meta-analysis

List of abbreviations: IFI: Invasive Fungal Infection; VLBW: Very Low Birth Weight; ELBW: Extremely Low Birth Weight; ROP: Retinopathy of Prematurity

Background

Invasive fungal infection (IFI) causes high morbidity and mortality in preterm infants. The incidence of IFI in each hospital varies. Research shows that the incidence of invasive candidiasis ranges from 2.6% to 13.2% in preterm very low birth weight (VLBW) infants (<1500 g) and from 6.6% to 26.0% in preterm extremely low birth weight (ELBW) infants (<1000 g) [1]. Invasive fungal infections has become the third most common cause of nosocomial infection in NICU in preterm VLBW infants [2]. Neonatal fungal infection has poor prognosis, severe IFI may be associated with severe retinopathy of prematurity (ROP), intracranial hemorrhage [3] and adverse neurodevelopmental outcome [4,5]. Since clinical manifestations of neonatal fungal infection are often not typical and lack specificity, it is very difficult to obtain an early diagnosis; delayed treatment increases the fatality rate. Thus prevention of IFI might be critical in helping these vulnerable VLBW infants.

In 2001, Kicklighter *et al.* [6] reported the first randomized controlled trial (RCT) that prophylactic use of fluconazole to prevent fungal colonization in VLBW infants. After then, multiple large-scale RCT were conducted in many countries [7-13]; however, prophylactic use of fluconazole to prevent fungal infection in preterm neonates is still controversial. There are still no solid conclusions or guidelines about the target population, efficacy and safety on prophylactic use of fluconazole in VLBW infants. Nonetheless, many pediatricians in NICU (15% to 34%) have adopted the prophylactic use of fluconazole to prevent fungal infection in preterm neonates in the United States and Britain [14]. Furthermore a recently study showed that prophylactic use of fluconazole reduce IFI by 66%. Overall mortality was similar between treatment groups, but 40% of patients with IFI died, so study underpowered for examine effect of prevention on mortality [7]. In 2013, a meta-analysis showed that prophylactic systemic antifungal therapy reduced the incidence of invasive fungal infection but did not demonstrate a statistically significant effect on mortality in VLBW infants [15]. However, the intervention strategy includes fluconazole, amphotericin B and nystatin. Subsequently to this systematic review, two RCTs [7,8] including prophylactic fluconazole versus placebo that involved 436 preterm neonates have been reported.

Given the global burden related to IFI in VLBW neonates and the reported of the very significant benefits of this low-cost, simple and easily available of prophylactic fluconazole in the prevention of IFI in this high risk group. An updated meta-analysis may help in clinical decision making regarding antifungal prophylaxis. Our aim was to do an update systematic review of randomized controlled trials (RCTs) to evaluate the efficacy and safety of prophylactic use of fluconazole in VLBW infants.

Materials and Methods

Inclusion and exclusion criteria

Inclusion criteria were articles that described randomized, placebo controlled clinical trials of preterm infants whose birth weight were less than 1500 grams and had high risk factors for fungal infection before enrollment but no diagnosis of fungal infection. Second, all patients in the experimental group were administered fluconazole for prevention of fungal infection. Results of the experimental group were compared with those in the placebo control group. Third, the rate of fungal colonization (fungus can be cultured from any tissue, but has not yet become fungal infection) or fungal infection (invasive fungal infections attacking deep tissue, internal organs, and the whole body, including infection in deep tissue, and fungemia) or mortality were compared between the two groups. Fourth, the safety of drugs and the changes of drug-resistant fungal spectrum had been observed. Exclusion criteria were tests without comparison group, or clinical trials with solely historical control or case control.

Search strategy

We searched the Cochrane Central Register of Controlled Trials, PUBMED, EMBASE, China National Knowledge Infrastructure, and Chinese Bio-medicine Database from database inception to December 2017, using a combination of the following text words and MeSH terms: preterm, very low birth weight, or extremely low birth weight, luconazole, prophylactic, fungus colonization, fungus infection. We did not apply any language restriction. Reference lists of eligible articles identified from this search were checked to reveal other potentially relevant trials.

Quality Assessment

We applied the Cochrane Risk of Bias tool to assess sequence generation [16]: allocation concealment; blinding of participant, personnel, and outcome assessor; attrition bias; incomplete outcome data; selective outcome reporting. Two reviewers (S-T L and B-Q L) assessed each criterion for bias: “yes” meant low risk of bias, “no” meant high risk of bias and “unclear” indicated unclear or unknown risk of bias. Any disagreement was resolved by discussion.

Data Extraction and Outcome measurement

Two reviewers (H H and M-X L) independently assessed publications for inclusion in the review. Discrepancies were resolved through discussion by the review team (n=5).

Primary outcomes were the incidence of fungal colonization and invasive fungal infection. Secondary outcomes included death from all causes prior to hospital discharge, emergence of antifungal resistance, and adverse drug reactions. Data on follow up and long-term development were retrieved.

Statistical analysis

The Cochrane Collaboration's Review Manager Software (RevMan Version5.2) was utilized for data analysis. The heterogeneity tests of trials were performed using I^2 tests [$P \leq 0.05$ indicated significant heterogeneity] and funnel plots. When the hypothesis of homogeneity was not rejected, we used the fixed effect model to estimate the pooled effects of safety and efficacy outcomes in the fluconazole group. Otherwise, random effect model was calculated. The results of dichotomous data were expressed as a relative risk (RR) and the risk difference (RD) with 95% confidence interval (95% CI). In addition, we performed subgroup analyses according to birth weight (<1000g).

Results

After the initial screening of abstracts and titles, 67 of 495 articles remained for full text review. Full text review excluded 59 articles due to improper intervention or not RCTs or insufficient data. Eight articles [6-13] met the inclusion criteria and exclusion criteria involving 1392 VLBW infants (Figure 1). The basic information of the RCTs was listed in Table 1.

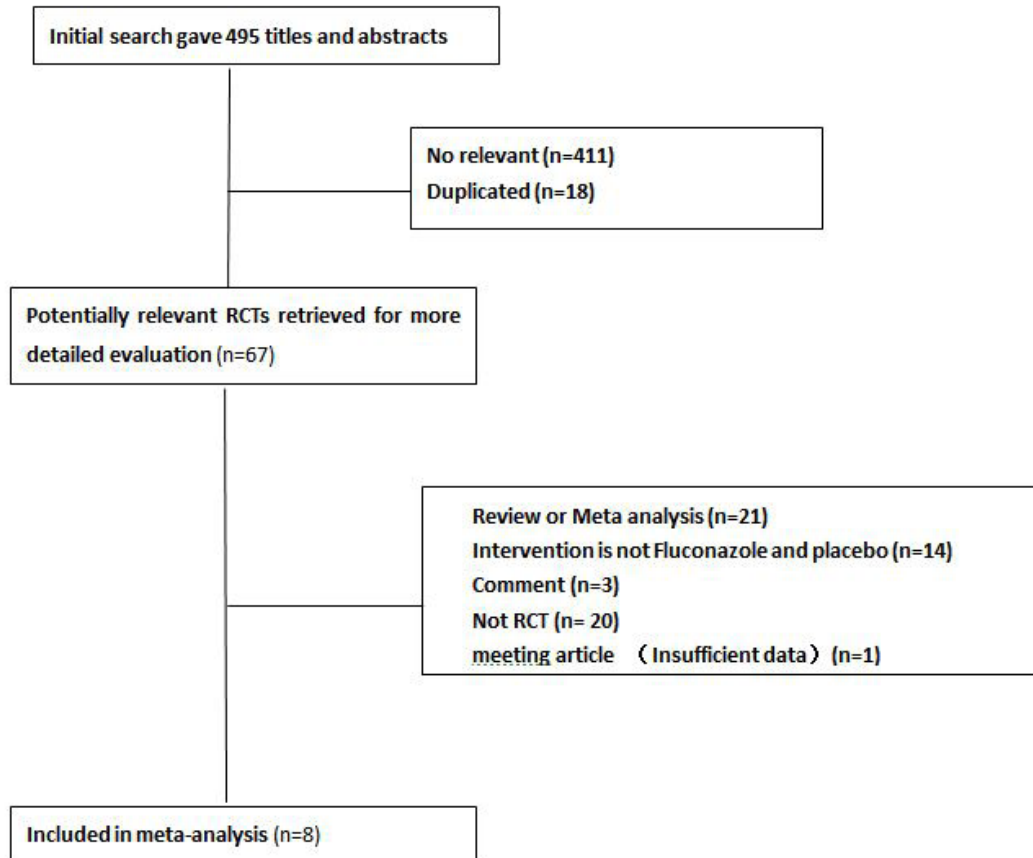


Figure 1: Selection of randomized controlled trials (RCTs) for the meta-analysis

Study	Country	Year	Fluconazole Intervention	Control
Kirpal [8]	India	2015	(N=38) intravenous 6 mg/kg every other day for 7 days then every day till day 28 of life or till discharge	(N=37) placebo
Benjamin [7]	USA	2014	(N=188) 6 mg/kg twice weekly for 42 days. Administered intravenously in infants with intravenous access, and enterally by orogastric tube to infants without intravenous access.	(N=173) normal saline
Aydemir [9]	Turkey	2011	(N=93) 3mg/kg one daily from third day, ELBW for 6 weeks, VLBW for 4 weeks. Administered intravenously in infants with intravenous access, or through an orogastric tube when enteral feeding was established.	(N=91) normal saline
WU [10]	China	2009	(N=63) oral 6mg/kg every 24 hours for 7 days	(N=64) milk
Parikh [11]	India	2007	(N=60) 6mg/kg every 72 hours daily for 8-28 days. Administered intravenously in infants with intravenous, then orally till baby reach full feeds.	(N=60) normal saline

Manzoni [12]	Italian	2007	(N=112) 6 mg or (N=104)3 mg /kg every third day for the first 2 weeks and then every other day ELBW for 6 weeks, VLBW for 4weeks. Administered intravenously in infants with intravenous access, or through an orogastric tube when enteral feeding was established .	(N=106) normal saline
Kicklighter [13]	USA	2001	(N=53) 6mg/kg/day every 72 hours for 7 days daily for 8-28days. Administered intravenously and then oro-gastrically when tolerated.	(N=50) normal saline
Kaufman [3]	USA	2001	(N=50) intravenous 3 mg/kg every third day for the first two weeks, then every second day during the third and fourth weeks, then daily during the fifth and sixth weeks, or until intravenous access discontinued.	(N=50) normal saline

Table 1: Basic characteristics of trials included in this study

Quality of the references

The details of the risk-of-bias assessment are summarized in Figure 2. The included trials were generally of good methodological quality. Six trials were judged to be at low risk of bias, 1 at unclear risk and 1 at high risk of bias. Although all eight trials mentioned random allocation, only 7 articles detailed the mechanism of random allocation and showed that allocation was concealed by separation of the randomization process from recruitment and enrollment. Caregivers, investigators, and assessors were blinded to the intervention in 6 articles. All trials reported complete assessment for primary outcomes and selective reporting.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aydemir 2011	+	+	?	?	+	+	+
Benjamin 2014	+	+	+	+	+	+	+
KAUFMAN 2001	+	+	+	+	+	+	+
Kicklighter 2001	+	+	+	+	+	+	+
Kirpal 2015	+	+	+	+	+	+	+
Manzoni 2007	+	+	+	+	+	+	+
Parikh 2007	+	+	+	+	+	+	+
wu 2009	?	?	-	-	+	+	+

Figure 2: Appraisal of risk of bias of the included trials using the Cochrane risk-of-bias tool

The effect of prophylactic use of fluconazole on the rate of fungal colonization

Six RCTs [6,9-13] involving 956 infants showed the effect of prophylactic use of fluconazole on the rate of fungal colonization. The six articles in the heterogeneity test ($I^2=0\%$, $P=0.94$) showed that the research had homogeneity: RR was 0.31 (95%CI:-0.24 to 0.41, $P<0.00001$) and RD was -0.25 (95%CI-0.30 to -0.20). The meta-analysis showed that prophylactic fluconazole administration decreased the rate of fungal colonization significantly (Figure 3). No evidence was found for funnel plot asymmetry (Figure 4).

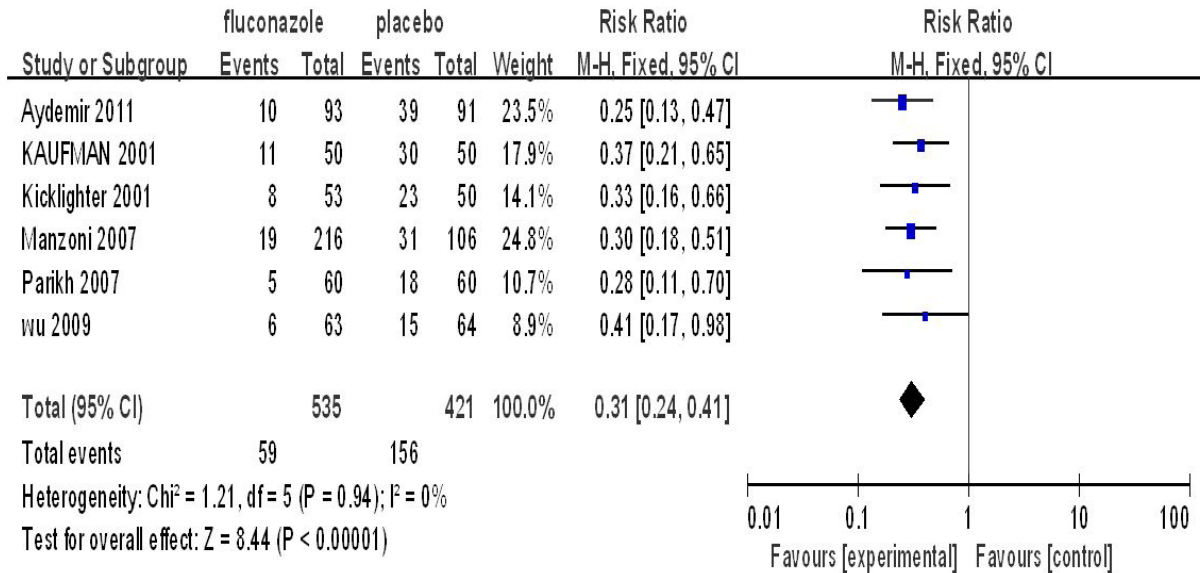


Figure 3: Forest plot of comparison: prophylactic use of fluconazole vs placebo on the incidence of fungal colonization

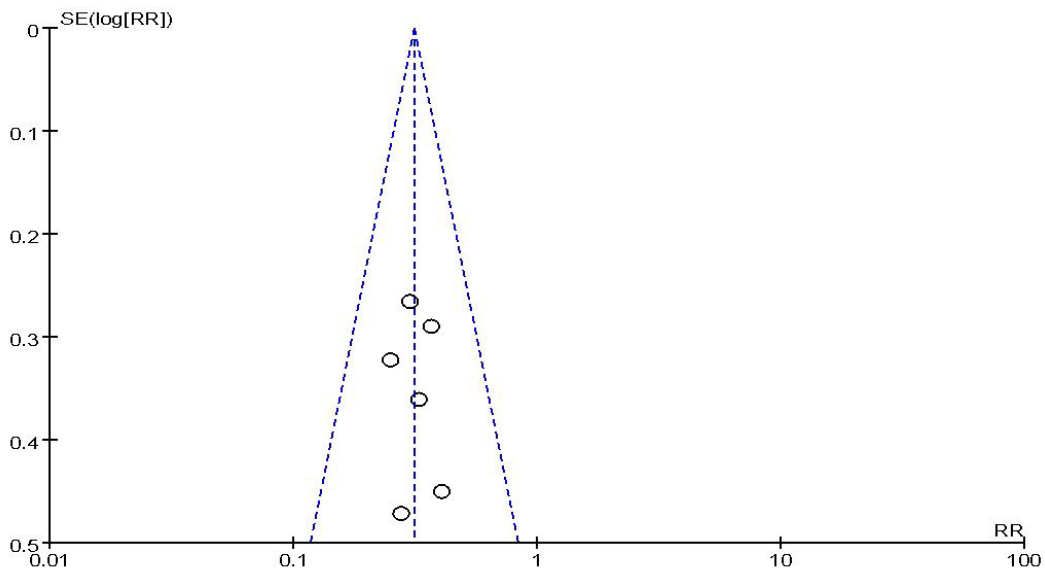


Figure 4: Funnel plot of the influence of prophylactic use of fluconazole on the incidence of fungal colonization in preterm VLBW infants

Subgroup analysis in extremely low birth weight infants (ELBW) infants showed the same pattern. (two trials [12,13]; RR, 0.33; 95% CI, 0.2 to 0.56; $P < 0.0001$; $I^2 = 0\%$, $P=0.49$)

Effect of prophylactic use of fluconazole on the rate of invasive fungal infection

The invasive fungal infection rate was documented in seven trials [6-9,11-13]. The 698 infants in the fluconazole group and the 567 infants in the control group experienced 44 and 91 invasive fungal infections, respectively. The heterogeneity test indicated heterogeneity, ($I^2=60\%$, $P=0.02$) and the RR was 0.42 (95%CI 0.23 to 0.76, $P=0.004$) by the random effects model. RD was -0.09 (95%CI -0.14to -0.04). The results showed that prophylactic use of fluconazole decreased the rate of fungal infection (Figure 5). There was evidence of statistical heterogeneity in this meta-analysis ($I^2 = 60\%$) but no evidence of funnel plot asymmetry (Figure 6). Parikh *et al.* [11] was the main source of the heterogeneity. Exclusion of Parikh’s study removed this heterogeneity (revised RR 0.31, 95% CI 0.21 to 0.47; revised $I^2 = 11\%$, $P=0.34$). Similarly, subgroup analysis of ELBW infants in the three trials [7,12,13]

showed that prophylactic fluconazole administration significantly reduced the rate of invasive fungal infections (RR, 0.27; 95% CI, 0.16 to 0.47; $P < 0.0001$; $I^2 = 10\%$, $P = 0.33$).

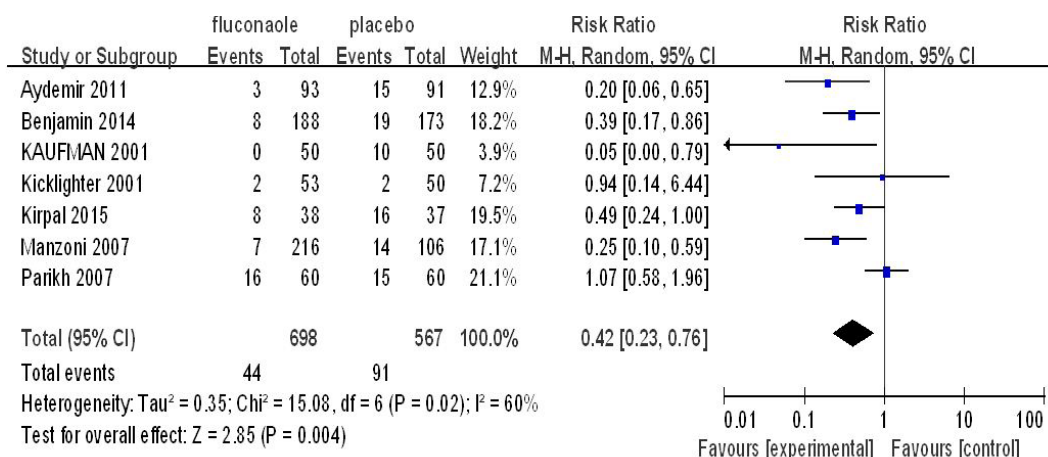


Figure 5: Forest plot of comparison: prophylactic use of fluconazole vs placebo on the incidence of invasive fungal infection

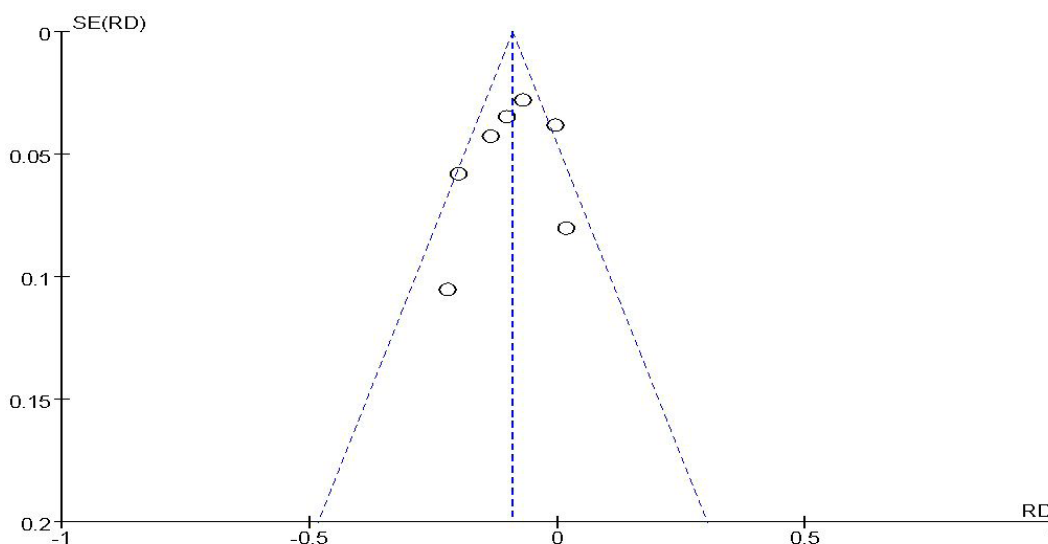


Figure 6: Funnel plot of the influence of prophylactic use of fluconazole on the incidence of invasive fungal infection in preterm VLBW infants

Effect of prophylactic use of fluconazole on the rate of mortality in VLBW infants

Seven studies [6-9,11-13] with 1265 infants were eligible for analysis of mortality. Meta-analysis of these seven trials using a fixed-effects model showed that prophylactic use of fluconazole did not reduce the mortality rate in VLBW infants (RR 0.76, 95% CI 0.58 to 1.01; $P = 0.06$) compared with controls, with little statistical heterogeneity between the trials ($I^2 = 0\%$, $P = 0.65$). RD was -0.04 (95%CI -0.08 to 0.00) (Figure 7). There was no evidence of funnel plot asymmetry (Figure 8). Subgroup analysis in ELBW infants in two trials [7,13] had similar findings (RR, 0.82; 95% CI, 0.55 to 1.23; $P = 0.34$; $I^2 = 52\%$, $P = 0.15$).

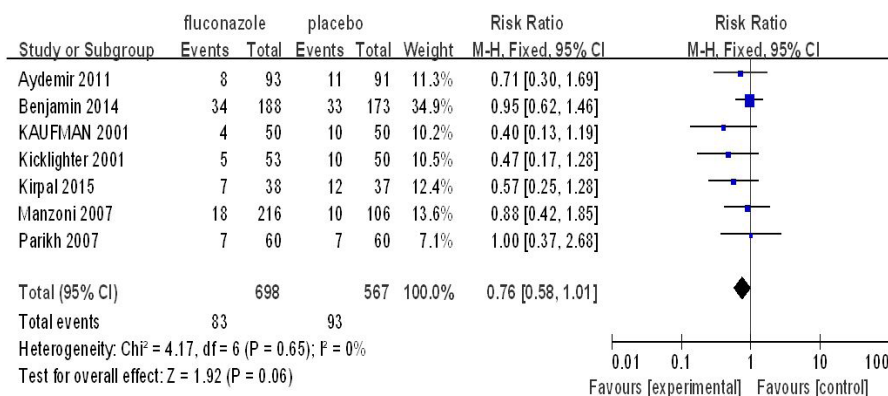


Figure 7: Forest plot of comparison: prophylactic use of fluconazole vs placebo on the incidence of mortality

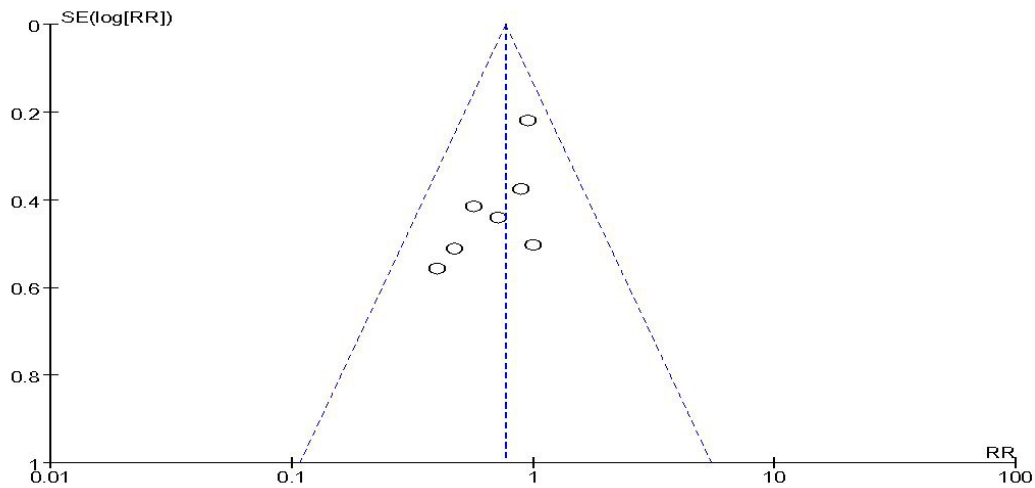


Figure 8: Funnel plot of the influence of prophylactic use of fluconazole on mortality in preterm VLBW infants

Effect of prophylactic use of fluconazole on fungal resistance

Analysis for fungal resistance was compared by minimal inhibitory concentration (MIC). The results showed that *Candida albicans* and *Candida parapsilosis* were sensitive to fluconazole in 4 studies [6,9,12,13] and that prophylactic use of fluconazole had no obvious selection for significantly higher MIC of *Candida sp.*

Adverse effects of fluconazole

Eight RCTs showed that there was no significant toxicity reported from fluconazole in the studies reviewed and no babies were withdrawn from the studies.

Effect of prophylactic use of fluconazole on long-term neurodevelopmental in VLBW infants

There were 2 papers mentioned long-term neurodevelopmental follow-up. Benjamin *et al.* [7] reported follow-up of the hospitalized children after 18 to 22 months (using corrected gestational age). They found that the incidence rate of neurodevelopment disorders, cerebral palsy, deafness, and blindness showed no difference between treated group and control group. Kaufman *et al.* [3] treated 50 patients in both groups, and there was no statistical significance in survival rate between the fluconazole group the control group. The 8 to 10 year follow-up showed no significant difference between patients in two groups in neurodevelopment and quality of life.

Discussion

This update meta-analysis suggests that prophylactic use of fluconazole can significantly reduce the rate of fungal colonization and IFI in VLBW infants. However, this meta-analysis revealed that prophylactic fluconazole did not significantly reduce the rate of mortality in VLBW infants (RR 0.76, 95% CI 0.58 to 1.01; $P = 0.06$); subgroup analysis in ELBW infants suggested that they did not differ in the rate of fungal colonization, invasive fungal infection, and mortality. Prophylactic fluconazole did not increase the occurrence of drug-resistant fungi nor change the rate of adverse effects (liver function damage and elevated bilirubin). Though prophylactic fluconazole did not decrease mortality due to studies were underpowered to detect this difference. Since IFI can lead to severe ROP and intracranial hemorrhage [3] and adverse neurodevelopmental outcome. Further study might focus these complications to emphasize the beneficial effects of prophylactic fluconazole in these vulnerable infants.

Fungal colonization is the highest risk factor of fungal infection in VLBW infants. Reducing colonization can decrease the rate of invasive fungal infection in VLBW infants [17]. A multicenter study found that the fungus colonized in patients' blood and the gastrointestinal tract was the same *Candida albicans* strain, which means that *Candida albicans* colonization can develop into invasive fungal infections [18]. Manzoni *et al.* reported that 23% of fungal infections in VLBW infants developed from fungal colonization in their body [19]. They also found that fungal skin colonization occurs in a significant proportion of VLBW infants (12–27%) in the first few weeks of life, usually with *Candida* species [19]. Kaufman *et al.* found that the fungus colonized the patients' skin, excrement, and throat more often [13]. Prophylactic use of fluconazole reduced the rate of fungal colonization and infection, but it had no effect on the rate of fungal colonization developing into deep-seated fungal infection [20,21]. Fungal colonization was found in 4.8% to 10% of VLBW infants' gastrointestinal tracts, and the rate of fungal colonization can increase to 50% to 64% at 1 week and 4 weeks after birth [22].

The studies of Kicklighter [6] and Parikh [11] reported that prophylactic use of fluconazole did not decrease the rate of fungal infection; nonetheless, they thought this might be due to an insufficient sample size to reach statistical significance and short follow-up.

This updated meta-analysis showed that the rate of mortality did not differ significantly between prophylactic fluconazole group of VLBW infants and the control group. Benjamin's study in 361 extremely low birth weight infants whose birth weight were all less than 750 grams showed that prophylactic use of fluconazole reduce Invasive candidiasis, but not decrease the incidence of the composite of death or invasive candidiasis in these infants [7]. However, the effect of prophylactic use of fluconazole on the rate of mortality in VLBW infants, it should be interpreted with caution. The rate of mortality was 11.9% in the prophylactic fluconazole treated group of 698 infants but was 16.4% in control group of 567 infants in seven RCTs; the P value 0.06 was almost significant [6-9,11-13]. However, five of the seven RCTs were not designed to study the effect of prophylactic fluconazole on the mortality rate in VLBW infants. Thus, we need to design RCT with sufficient sample size (statistical power) to detect a significant difference in mortality rate and with mortality rate as a secondary outcome.

The major concern with prophylactic use of fluconazole is the occurrence of drug-resistant fungi and *Candida albicans*. This study found no drug-resistant fungi after prophylactic use of fluconazole and no marked change in MIC against *Candida albicans*, in agreement with Healy's study [23] and Manzoni *et al.* [24] in VLBW infants. In contrast, prophylactic fluconazole use in children and adults has promoted an increase in fungal resistance, and part of the fungal species did not belong to *Candida* [25,26]. Fluconazole has been prophylactically used for 6 years in NICUs of Parikh, India [11]. The studies in 2003 to 2004 showed that 96.8% of neonatal fungal infection was not caused by *Candida*. Sarvikivi *et al.* [27] found that fluconazole has been prophylactically used for 12 years in their NICU, and they detected *Candida parapsilosis*, which is not sensitive to fluconazole. As prophylactic use of fluconazole has become routine in their NICU, the common fungal infection spectrum has changed, which leads to more difficulties in treatment. In our meta-analysis, each clinical trial had a short follow-up time and small sample size; these limitations may obscure our ability to detect drug-resistant fungi and fungal infections. Thus, further research is needed to assess whether prophylactic use of fluconazole in VLBW infants increases drug-resistance or selects for nonsensitive strains.

Prophylactic use of fluconazole in VLBW infant can decrease the rate of fungal colonization and fungal infection significantly, but the medical decision of its routine use might depend upon the incidence rate of fungal infection in each NICU. If the the rate of fungal infection are high, prophylactic use of fluconazole could provide sufficient benefit in comparison to the risks. Hospitals and physicians should minimize drug-resistance as much as possible by strictly following the indications and paying attention to VLBW infants of high risk. Secondly, hospitals and physicians should monitor the spectrum of fungal infection after several years of prophylactic use of fluconazole, initiate follow-up of fungal infection, track the incidence of drug-resistant fungi, and adjust treatment as needed.

Two limitations in this meta-analysis were the variable prophylactic protocol and the short term follow-up. The variable prophylactic protocol as dosage, interval, and duration of fluconazole were a little bit different among the enrolled RCTs. Secondary, since development of drug-resistant fungi requires sufficient time for selection and growth, appearance of certain drug-resistant fungi should be assessed at long term follow-up in future studies.

Conclusion

Based on the meta-analysis of eight RCTs, we conclude that the incidence of fungal colonization and invasive fungal infection in VLBW infants could be significantly reduced by prophylactic fluconazole. Further studies should focus on the efficacy of prophylactic fluconazole on preterm ELBW infants, rate of morbidity, and mortality and long term neurodevelopmental outcomes with adequate sample size.

Authors' contributions

STL and H H conceived the idea and prepared a draft review protocol. STL, MXL, YC, BQL were responsible for literature search and retrieving data. STL and H H analyzed the data and prepared the manuscript. X X supervised the calculation of the effect sizes and the performance of meta-analyses. CHL performed interpretation of analyses and critically revised the paper. All authors read and approved the final manuscript.

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