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# **BMJ Open**

#### Clinical outcomes of antifungal therapy on Candida pulmonary colonization in immunocompetent patients with invasive ventilation: A systematic review and meta-analysis

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# Clinical outcomes of antifungal therapy on Candida pulmonary colonization in immunocompetent patients with invasive ventilation: A systematic review and meta-analysis

Keywords: *Candida* colonization, pulmonary, antifungal therapy, mechanical ventilation, meta analysis.

#### 3 Abstract

Objective: This study aimed to use systematic review and meta-analysis to establish the
 influence of antifungal therapy on pulmonary *Candida* colonization of patients with mechanical
 ventilation.

8 Data sources: An extensive search was undertaken on publications from inception to July 25,
9 2023, through PubMed, Web of Science, Medline, Embase, China National Knowledge
10 Infrastructure, Wanfang Data and VIP Databases.

Eligibility criteria for selecting studies: Randomized trials, cohort studies, and case-control
 studies comparing the efficacy of antifungal treatment in immunocompetent patients with pulmonary
 *Candida* colonization after invasive ventilation.

Data extraction and synthesis: Two reviewers independently extracted the data and assessed
 the quality of studies. Dichotomous outcomes were expressed as odds ratios (OR) with 95%
 confidence intervals (CIs). Continuous outcomes were expressed as standard mean differences
 (SMD) with 95% CIs.

Primary and secondary outcome measures: The primary outcomes included ICU, hospital,
 28-day, and 90-day mortality. The secondary outcomes included ICU length of stay, MV duration,
 and VAP.

**Results:** Nine high-quality studies were included. According to the data collected from these nine studies, there is no significant evidence showing a difference between the therapy group treated with antifungal drugs and the control group without antifungal drugs in clinical outcomes, including intensive care unit mortality (OR: 1.37; 95% CI, 0.84 to 2.22), hospital mortality (OR: 1.17; 95% CI, 0.57 to 2.38), 28-day mortality (OR; 0.71, 95% CI, 0.45 to 1.14), 90-day mortality (OR; 0.76, 95% CI 0.35 to 1.63), intensive care unit length of stay (SMD: -0.15; 95% CI -0.88 to 0.59), mechanical ventilation duration (SMD: 0.11; 95%CI -0.88 to 1.10), and ventilator-associated pneumonia (OR: 1.54; 95% CI 0.56 to 4.20). Subgroup analysis of different treatment types indicate that the combined effect size is stable and unaffected by different treatment types including inhalation (OR: 2.32; 95% CI 0.30 to 18.09) and intravenous (OR: 0.65; 95% CI 0.13 to 3.34). 

Solution: The application of antifungal treatment did not improve clinical outcomes in patients with mechanical ventilation. We do not suggest initiating antifungal treatment in patients with *Candida* pulmonary colonization after invasive ventilation.

**Design:** Systematic review and meta-analysis.

**Registration:** This study was registered in the International Prospective Register of Systematic Reviews, with the registration number CRD42020161138.

Strengths and limitations of this study: This meta-analysis has a number of outcome indicators to evaluate the effect of antifungal treatment. Subgroup analysis was conducted based on the treatment type which showed a stable result. However, in quoted and analyzed references, some studies declared whether they included patients with pre-existing pneumonia, while others did not. Second, some studies described the precise style, name, dose, and administration method of antifungal drugs, while others did not. Third, it is important to encourage future research endeavors to enhance the quality of this meta-analysis. This can be achieved by incorporating an expanded array of studies, distinguished by a larger sample size, and meticulously defined inclusion and exclusion criteria. 

#### Introduction

Candida frequently exists in the normal oral cavity, upper respiratory tract, lower-intestinal tract and vagina(1). In tracheal aspirates from patients with mechanical ventilation (MV), 30% have *Candida* isolation, and nearly 50% from patients suspected to have a ventilator-associated pneumonia (VAP)(2). When respiratory *Candida* colonization is detected, it is difficult to differentiate between relatively harmless colonization and invasive infection, and leads to a therapeutic dilemma(3). Although few studies reported limited attributable ICU mortality of VAP, the death rate related to VAP can not be denied according to the mojority of previous studies(4-7). The presence of *Candida* in respiratory samples is defined as *Candida* colonization instead of infection because the appearance of Candida pneumonia is rare(8-10). For several years, arguments arose about whether Candida colonization negatively affected or simply symbolized disease severity or immunosuppression in critically ill patients(11-13). We found that the outcomes of antifungal treatment for *Candida* colonization in pulmonary tract among different studies were controversial, as some studies found that antifungal treatment is associated with lower mortality, some found that treatment made no difference in mortality, while others found that it prolonged MV duration, intensive care unit (ICU) length of stay, and hospital length of stay(8, 9, 14, 15). Therefore, we performed a systematic review and meta-analysis to establish the influence of antifungal treatment on pulmonary Candida colonization. 

#### Method

#### 2.1 Information sources and search strategy

This study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis criteria for systematic reviews and meta-analyzes. An extensive search was undertaken on publications from inception to July 25, 2023, through PubMed, Web of Science, Medline, Embase, China National Knowledge Infrastructure, Wanfang Data and VIP Databases. The searching syntax included the following Medical Subject Headings (Mesh) and text words which are varied individually according to different databases: ventilator-associated pneumonia. *Candida*. We used the following search strategies: (ventilator-associated pneumonia OR VAP OR pneumonia, ventilator-associated OR ventilator-associated pneumonia OR ventilator-acquired pneumonia OR mechanical ventilation) AND (Candida OR Candida spp OR Candida colonization OR Candida airway colonization). There were no language restrictions on studies searching. The listed references of relevant studies were also evaluated to enlarge the search scope and ensure a complete search. 

#### 2.2 **Inclusion criteria**

<sup>2</sup> 76 Selection process of the article was performed by two researchers (LL and SS) independently, the
 <sup>3</sup> 77 titles and abstracts of the entries identified in the search were screened. Full text version of all articles

<sup>4</sup> 78 that potentially met the eligibility criteria to make a decision. Disagreements, if any, were resolved

<sup>5</sup> <sup>6</sup> <sup>79</sup> through discussion with a third researcher (HX). Randomized trials, cohort studies, and case-control

80 studies were included. In the included studies, the patients were adults ( $\geq 18$  years old) who were 81 diagnosed with pulmonary *Candida* colonization after invasive ventilation. Pulmonary *Candida* 

8 81 diagnosed with pulmonary *Candida* colonization after invasive ventilation. Pulmonary *Candida* 9 82 colonization was defined as the presence of *Candida* in bronchoalveolar lavage samples,

endotracheal aspiration samples, protected brush specimens, or any positive airway secretion

<sup>11</sup> 84 specimens.

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#### 85 2.3 Exclusion criteria

15 86 We excluded case reports and studies on pregnant, immunocompromised patients, or received 16 antifungal treatment for reasons other than *Candida* colonization. Patients with candidemia or 87 17 invasive candidiasis were also excluded, and the diagnostic criteria were positive results of direct 88 18 detection, in which blood or tissue specimens were cultured, or indirect detection, in which surrogate 89 19 markers and polymerase chain reaction assays were used (16). 20 90

#### 91 2.4 Data collection

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## <sup>29</sup>30 96 2.5 Quality assessment

We used the Cochrane risk assessment tool to measure the risk of randomized controlled trials and
the Newcastle-Ottawa Scale to measure the quality of cohort and case-control studies. Studies that
scored at least six points were regarded as high-quality and included.

# <sup>36</sup> 100 <sup>37</sup> 2.6 Statistical analysis

38 101 Dichotomous outcomes such as VAP, ICU mortality, hospital mortality, 28-day mortality, and 90-39 102 day mortality, were expressed as odds ratios (OR) with 95% confidence intervals (CIs). Continuous 40 103 outcomes (ICU length of stay and MV duration) were expressed as standard mean differences with 41 104 95% CIs. We analyzed the data using the Inverse-Variance method with the fixed-effect model if 42 there was no obvious heterogeneity (P>0.1), or else random-effect model if the heterogeneity was 105 43 106 significant (P<0.1). Moreover, heterogeneity was quantified using the  $I^2$  test. The interpretation of  $I^2$ 44 was guided by the Cochrane Handbook for Systematic Reviews of interventions (Version 5.2.0, 45 107 46 108 updated June 2017).  $I^2$  range from 0 % to 40% indicates that the heterogeneity might not be 47 109 important;  $I^2$  range from 30 % to 60 % may represent moderate heterogeneity;  $I^2$  range from 50 % to 48 110 90 % may represent substantial heterogeneity; I<sup>2</sup> range from 75 % to 100 % indicates considerable 49 heterogeneity. Publication bias was not assessed since there were less than 10 studies in this meta-111 50 112 analysis. 51

#### 52 53 113 **3 Results**

#### 55 114 **3.1 Study selection**

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In total, 2947 records were identified. With 1246 duplicates removed and 1670 irrelevant records excluded, we assessed 31 studies for eligibility, of which 9 were included. 22 studies should not be included because of the lack of antifungal treatment, lack of supporting experimental data, lack of detection of pulmonary secretion, and occurrence in a special population (Figure 1). All patients received MV, had at least one positive culture of *Candida* in the pulmonary tract, and received different antifungal treatments. Figure 1 Flowchart of studies identified, excluded, and included 3.2 Study characteristics and quality assessment Of the nine articles included in the study, seven were retrospective cohort studies, one case-control study, and one randomized clinical trial. Two studies were conducted in North America, five in Europe, and two in Asia, giving the studies a wide geographical coverage. Other characteristics of the included studies are summarized in Supplemental Table 1, including years of accuracy, location, study style, population, number of patients, outcomes, *Candida* colonization and antifungal treatment. The columns of the quality assessment list and their corresponding points are listed in Supplemental Table 2. All included studies were assessed to be of high quality. 3.3 Effect of antifungal therapy on pulmonary *Candida* colonization patients' mortality Three studies, including Ioannou 2021(2), Ong 2013(17), and Nseir 2007(18) reported ICU mortality. We found no significant difference between the therapy and control groups (OR: 1.37, 95% CI, 0.84 to 2.22). Six studies, including Du 2021(3), Ioannou 2021, Zhang 2017(19), Griffin 2016(20), Lindau 2015(21), and Albert 2014(22) reported hospital mortality. The pooled results showed no significant difference between the therapy and control groups (OR: 1.17, 95% CI, 0.57 to 2.38). Four studies, including Du 2021, Zhang 2017, VanDerGeest 2014(23), and Albert 2014, reported 28-day mortality. The results showed no significant difference between the therapy and control groups (OR: 0.71, 95%) CI, 0.45 to 1.14). Three studies, Du 2021, VanDerGeest 2014, and Albert 2014, reported 90-day mortality. The results showed no significant difference between the therapy and control groups (OR: 0.76, 95% CI, 0.35 to 1.63). No indicator showed statistical significance with respect to mortality. (Figure 2) Figure 2 (A) Forest plot for ICU mortality; (B) Forest plot for hospital mortality; (C) Forest plot for 28-day mortality; (D) Forest plot for 90-day mortality 3.4 Effect of antifungal therapy on pulmonary Candida colonization patients' ICU length of stav Four studies, including Zhang 2017, Griffin2016, Ong 2013, and Nseir 2007, reported ICU length of stay. The results indicated non-significant results for ICU length of stay among patients receiving antifungal treatment (SMD: -0.15, 95% CI, -0.88 to 0.59), as shown in Figure 3. Figure 3 Forest plot for ICU length of stay 3.5 Effect of antifungal therapy on pulmonary *Candida* colonization patients' MV duration Three studies, including Zhang 2017, Griffin 2016, and Nseir 2007, reported the duration of MV. We did not identify a significant difference between the therapy and control groups regarding MV duration (SMD: 0.11, 95%CI, -0.88 to 1.10), as shown in Figure 4. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml 

Page	6	of	2
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1 2	154	Figure 4 Forest plot for MV duration
3 4	155	<b>3.6 Effect of antifungal therapy on VAP</b>
5 6 7 8 9	156 157 158	Six studies, including Du 2021, Zhang 2017, Griffin 2016, Lindau 2015, VanDerGeest 2014, and Ong 2013, reported VAP. No significant difference was found between therapy and control groups (OR: 1.54, 95% CI, 0.56 to 4.20), as shown in Figure 5.
10 11	159	Figure 5 Forest plot for VAP
12 13	160	3.7 Subgroup analysis
14 15 16 17	161 162 163	We conducted a subgroup analysis based on effect of antifungal therapy on VAP of the included studies. The result of the subgroup analysis indicate that the combined effect size is stable and unaffected by different treatment types. As shown in Supplemental Figure 1.
10 19 20	164	Supplemental Figure 1 Forest plot for subgroup analysis of different treatment types
20 21 22	165	3.8 Sensitivity analysis and publication bias
23 24 25 26 27 28 29	166 167 168 169 170	A sensitivity analysis was performed by sequentially excluding one study at a time. This exclusion did not significantly impact the results, with the pooled OR ranging from 1.00 (0.51-1.96) to 2.07 (0.74-5.78) (Supplemental Figure 2). Because only 9 related studies were included in this report, approaches for detecting publication bias would have exhibited limited efficacy. Consequently, the evaluation of publication bias was not conducted.
30 31	171	Supplemental Figure 2 Sensitivity analysis for VAP
32	172	4 Discussion
<ul> <li>33</li> <li>34</li> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> <li>50</li> <li>51</li> <li>52</li> <li>53</li> <li>54</li> <li>55</li> </ul>	173 174 175 176 177 178 179 180 181 182 183 184 185 186 187 188 189 190	In this study, we observed that antifungal therapy administered to mechanically ventilated patients with <i>Candida</i> colonization did not show a significant impact on patient outcomes, which were measured by indicators including mortality, hospital length of stay, ICU length of stay, mechanical ventilation duration, and incidence of VAP, and the result is stable when taking different treatment types into consideration. A study by Du declared that antifungal treatment was associated with a reduced risk of VAP, while an autopsy study involving 232 samples showed that although <i>Candida</i> is a common pathogen, the incidence of <i>Candida</i> pneumonia in ICU patients is extremely low(3, 9). Inconsistent with the results of the previous studies, a meta-analysis found that <i>Candida</i> pulmonary colonization probably had poorer clinical outcomes owing to longer mechanical ventilation duration, higher 28-day mortality, higher ICU mortality, and longer ICU length of stay(24). Furthermore, a study by Ioannou found that about half of the patients with <i>Candida</i> spp. isolation from their respiratory secretions were treated with antifungals more often, a multivariate regression analysis was conducted identifying antifungal use as an independent factor associated with total hospital mortality(2). Without listing the specific articles for verification, the guideline strongly recommends that <i>Candida</i> colonization rarely requires treatment with antifungal therapy(25). Our study, may help to provide more information on this problem: whether <i>Candida</i> pulmonary colonization simply symbolizes the severity of diseases or actually have influence on outcomes(26, 27).
55 56	191	<i>Candida</i> colonization in the respiratory tract is related to higher inflammation and may accelerate the disease process(28, 20). A faw studies used inhelation of antifungal drugs as therapy, which didn't
57 58	192	disease process(28, 29). A few studies used initiation of antifungal drugs as therapy, which didn't

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# show significant influence on patients' outcome. This may lead to direct inhibition or damage of the alveolar-capillary membrane, resulting in an influx of surfactant-inactivating plasma proteins(17, 23). After Can dida calorization, surrant increases in antifunced days resistance in Can dida and and

- <sup>4</sup> 195 After *Candida* colonization, current increases in antifungal drug resistance in *Candida* spp. and
- clinical treatment failures are of concern(30). Previous history of antifungal prescription influences
   *Candida* species distribution and susceptibility profile to antifungal agents(31). Inadequate dose and
- 7 197 Candida species distribution and susceptibility profile to a
   8 198 treatment failure may contribute to high mortality(32).

9 199 Considering the various conditions, we thought that various factors cause poor clinical outcomes: 10 11 200 antifungal treatment may have more harm than benefit in clinically ill patients. Different antifungal 12 drugs can have varying sensitivities or resistances as well as potential toxicity or adverse effects. 201 13 202 Inadequate dosing of antifungal drugs may also be a contributing factor. In short, further studies 14 203 should be conducted to verify their influence. Considering retrospective and current studies can only 15 204 provide hypotheses to prove the existence of a correlation, a prospective randomized controlled trial 16 205 may be a more appropriate solution to explore the effect of antifungal treatment on patients with 17 206 respiratory *Candida* colonization in combination with mechanical ventilation. 18

20 207 Based on the findings of this meta-analysis, the use of antifungal medication on mechanical-21 208 ventilated patients with respiratory *Candida* colonization does not appear to improve patients' 22 209 clinical outcomes. No significant differences were observed in ICU mortality, hospital mortality, 28-23 210 day mortality, 90-day mortality, ICU length of stay, MV duration, and VAP associated with different 24 treatment regimens. Further analysis of subgroups based on different treatment types confirmed these 211 25 conclusions. Therefore, the use of antifungal medication is not recommended for the decolonization 212 26 27 213 of mechanical-ventilated patients with respiratory Candida colonization. 28

**29** 214 **5 Author Contributions** 30

HX and HY provided article ideas and completed a literature search. LL and SS contributed to the
data analysis and manuscript writing.

#### 217 6 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

- 402207Patient and public involvement41
- Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination
   plans of this research.
- <sup>45</sup><sub>46</sub> 2238 Patient consent for publication
- <sup>47</sup> <sub>48</sub> 224 Not applicable.
- 49 50 225 **9 Ethics approval**
- 52 226 Not applicable.
- <sup>54</sup> 227 10 Data Availability Statement
   <sup>55</sup>
- The raw data of this study can be obtained from corresponding author under reasonable request.

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Figure 1 Flowchart of studies identified, excluded, and included

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Figure 2 (A) Forest plot for ICU mortality; (B) Forest plot for hospital mortality; (C) Forest plot for 28-day mortality; (D) Forest plot for 90-day mortality

569x373mm (96 x 96 DPI)

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Figure 4 Forest plot for MV duration

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Page 21 of	20				BMJ Open			36/bmjo cted by		
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# **BMJ Open**

#### Clinical outcomes of antifungal therapy on Candida pulmonary colonization in immunocompetent patients with invasive ventilation: A systematic review and meta-analysis

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Manuscript ID	bmjopen-2024-083918.R1
Article Type:	Original research
Date Submitted by the Author:	26-Aug-2024
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<b>Primary Subject Heading</b> :	Intensive care
Secondary Subject Heading:	Evidence based practice
Keywords:	Meta-Analysis, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Pulmonary Disease < Lung Diseases





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# Clinical outcomes of antifungal therapy on Candida pulmonary colonization in immunocompetent patients with invasive ventilation: A systematic review and meta-analysis

 Keywords: *Candida* colonization, pulmonary, antifungal therapy, mechanical ventilation, metaanalysis.

### 3 Abstract

**Objective:** This study aimed to use systematic review and meta-analysis to establish the 5 influence of antifungal therapy on pulmonary *Candida* colonization of patients with mechanical 6 ventilation.

**Design:** Systematic review and meta-analysis.

**Data sources:** An extensive search was undertaken on publications from inception to July 25,
2023, through PubMed, Web of Science, Medline, Embase, China National Knowledge
Infrastructure, Wanfang Data and VIP Databases.

Eligibility criteria for selecting studies: Randomized trials, cohort studies, and case-control
 studies comparing the efficacy of antifungal treatment in immunocompetent patients with pulmonary
 *Candida* colonization after invasive ventilation.

14 Data extraction and synthesis: Two reviewers independently extracted the data and assessed 15 the quality of studies. Dichotomous outcomes were expressed as odds ratios (OR) with 95% 16 confidence intervals (CIs). Continuous outcomes were expressed as standardized mean differences 17 (SMD) with 95% CIs.

Primary and secondary outcome measures: The primary outcomes included intensive care
 unit (ICU), hospital, 28-day, and 90-day mortality. The secondary outcomes included ICU length of
 stay, mechanical ventilation (MV) duration, and ventilator-associated pneumonia (VAP).

**Results:** Nine high-quality studies were included. According to the data collected from these nine studies, there is no significant evidence showing a difference between the therapy group treated with antifungal drugs and the control group without antifungal drugs in clinical outcomes, including intensive care unit mortality (OR: 1.37; 95% CI, 0.84 to 2.22), hospital mortality (OR: 1.17; 95% CI, 0.57 to 2.38), 28-day mortality (OR; 0.71, 95% CI, 0.45 to 1.14), 90-day mortality (OR; 0.76, 95% CI 0.35 to 1.63), intensive care unit length of stay (SMD: -0.15; 95% CI -0.88 to 0.59), mechanical ventilation duration (SMD: 0.11; 95%CI -0.88 to 1.10), and ventilator-associated pneumonia (OR: 1.54; 95% CI 0.56 to 4.20). Subgroup analysis of different treatment types indicates that the combined effect size is stable and unaffected by different treatment types including inhalation (OR: 2.32; 95% CI 0.30 to 18.09) and intravenous (OR: 0.65; 95% CI 0.13 to 3.34). 

Solution: The application of antifungal treatment did not improve clinical outcomes in patients with mechanical ventilation. We do not suggest initiating antifungal treatment in patients with *Candida* pulmonary colonization after invasive ventilation.

34	Registration: This study was registered in the International Prospective Register of Systematic
35	Reviews, with the registration number CRD42020161138.

- 36 Strengths and limitations of this study:
- This study included a number of outcome indicators to assess the effectiveness of antifungal
   treatment, with subgroup analyses performed based on the type of treatment administered.
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   11 39
   2. Most studies included are retrospective studies, raising potential concerns regarding their
   12 40 external validity.
- 41 3. Some studies described the precise style, name, dose, and administration method of antifungal
   42 drugs, while others did not.
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   5. Most studies included were cohort studies instead of random contral trials, which provide stronger evidence.

#### 24 47 **1** Introduction

*Candida* frequently exists in the normal oral cavity, upper respiratory tract, lower-intestinal tract and vagina(1). In tracheal aspirates from patients with MV, 30% have Candida isolation, and nearly 50% from patients suspected to have a VAP(2, 3). When respiratory *Candida* colonization is detected, it is difficult to differentiate between relatively harmless colonization and invasive infection, and leads to a therapeutic dilemma(4). Although few studies reported limited attributable ICU mortality of VAP, the death rate related to VAP cannot be denied according to the majority of previous studies(5-8). The incidence of VAP frequently extends hospital stay, elevates the economic burden, and raises the mortality rate(9). The presence of *Candida* in respiratory samples is defined as *Candida* colonization instead of infection because the appearance of *Candida* pneumonia is rare(10-13). For several years, arguments have arisen about whether *Candida* colonization negatively affects or simply indicates disease severity or immunosuppression in critically ill patients (14-16). We found that the outcomes of antifungal treatment for *Candida* colonization in pulmonary tract among different studies were controversial, as some studies found that antifungal treatment was associated with lower mortality, some found that treatment made no difference in mortality, while others found that it prolonged MV duration, intensive care unit (ICU) length of stay, and hospital length of stay(10, 11, 17, 18). Therefore, we performed a systematic review and meta-analysis to establish the influence of antifungal treatment on pulmonary Candida colonization. 

### 65 2 Method

### 66 2.1 Information sources and search strategy

This study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis criteria for systematic reviews and meta-analyzes. An extensive search was undertaken on publications from inception to July 25, 2023, through PubMed, Web of Science, Medline, Embase, China National Knowledge Infrastructure, Wanfang Data and VIP Databases. The searching syntax included the following Medical Subject Headings (MeSH) and text words which are varied individually according to different databases: ventilator-associated pneumonia, Candida. We used the following search 

strategies: (ventilator-associated pneumonia OR VAP OR pneumonia, ventilator-associated OR

- <sup>3</sup> 74 ventilator-associated pneumonia OR ventilator-acquired pneumonia OR mechanical ventilation)
- <sup>4</sup> 75 AND (*Candida* OR *Candida* spp OR *Candida* colonization OR *Candida* airway colonization). There
- 76 were no language restrictions on studies searching. The listed references of relevant studies were also
- 77 evaluated to enlarge the search scope and ensure a complete search. Selection process of the article
   78 was performed by two researchers (LL and SS) independently. The titles and abstracts of the entries
- 9 79 identified in the search were screened. Full text version of all articles that potentially met the
- 80 eligibility criteria was reviewed to make a decision. Disagreements, if any, were resolved through
   81 discussion with a third researcher (HX).

## 13<br/>1482**2.2**Inclusion criteria

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15 83 Randomized trials, cohort studies, and case-control studies were included while selecting. In the 16 84 included studies, the patients were adults (>18 years old) who were diagnosed with pulmonary 17 85 Candida colonization after invasive ventilation. Pulmonary Candida colonization was defined as the 18 presence of *Candida* in bronchoalyeolar layage samples, endotracheal aspiration samples, protected 86 19 brush specimens, or any positive airway secretion specimens. 20 87 21

# 22 88 **2.3 Exclusion criteria**

24 89 We excluded case reports and studies on pregnant, immunocompromised patients, or those who 25 90 received antifungal treatment for reasons other than Candida colonization. Patients with candidemia 26 91 or invasive candidiasis were also excluded, and the diagnostic criteria were positive results of direct 27 92 detection, in which blood or tissue specimens were cultured, or indirect detection, in which surrogate 28 markers and polymerase chain reaction assays were used(19). 93 29

### 94 2.4 Data collection

32 95 We screened titles and abstracts, reviewed the full text, and extracted data using an Excel sheet 33 (Microsoft Corporation). We primarily collected the characteristics of title, author, journal, year, 34 96 35 97 type, participants, inclusion or exclusion criteria, interventions, and clinical outcomes. Clinical 36 98 outcomes included 28-day mortality, 90-day mortality, ICU mortality, hospital mortality, ICU length 37 99 of stay, MV duration, and VAP. Disagreements were resolved by discussion with a third reviewer if 38 100 necessary. 39

# <sup>40</sup>41 101 2.5 Quality assessment

We used the Cochrane risk assessment tool to measure the risk of randomized controlled trials and
the Newcastle-Ottawa Scale to measure the quality of cohort and case-control studies(20). Studies
that scored at least six points were regarded as high-quality and included.

## <sup>47</sup> 105 **2.6** Patient and public involvement <sup>48</sup>

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination
 plans of this research.

## <sup>52</sup><sub>53</sub> 108 **2.7 Statistical analysis**

Statistical analysis was performed by Stata software (Version 16.0). Dichotomous outcomes such as
 VAP, ICU mortality, hospital mortality, 28-day mortality, and 90-day mortality, were expressed as
 OR with 95% CIs. Continuous outcomes (ICU length of stay and MV duration) were expressed as

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- interpretation of  $I^2$  was guided by the Cochrane Handbook for Systematic Reviews of interventions (Version 5.2.0, updated June 2017). Sensitivity analyses was conducted by excluding one study at a time from the analysis to assess the stability of the results. Publication bias was not assessed since there were fewer than 10 studies in this meta-analysis. Results 3.1 **Study selection** In total, 2947 records were identified. With 1246 duplicates removed and 1670 irrelevant records excluded, we assessed 31 studies for eligibility, of which 9 were included. 22 studies were excluded because of the lack of antifungal treatment, lack of supporting experimental data, lack of detection of pulmonary secretion, and occurrence in a special population (Figure 1). All patients received MV, had at least one positive culture of *Candida* in the pulmonary tract, and received different antifungal treatments. Figure 1 Flowchart of studies identified, excluded, and included 3.2 Study characteristics and quality assessment Of the nine articles included in the study, seven were retrospective cohort studies, one case-control study, and one randomized clinical trial. Two studies were conducted in North America, five in Europe, and two in Asia, giving the studies a wide geographical coverage. Other characteristics of the included studies are summarized in Supplemental Table 1, including years of accuracy, location, study design, population, number of patients, outcomes, *Candida* colonization and antifungal treatment. The columns of the quality assessment list and their corresponding points are listed in Supplemental Table 2. All included studies were assessed to be of high quality. 3.3 Effect of antifungal therapy on pulmonary *Candida* colonization patients' mortality Three studies, including Ioannou 2021(2), Ong 2013(21), and Nseir 2007(22) reported ICU mortality. We found no significant difference between the therapy and control groups (OR: 1.37, 95% CI, 0.84 to 2.22). Six studies, including Du 2021(4), Ioannou 2021, Zhang 2017(23), Griffin 2016(24), Lindau 2015(25), and Albert 2014(26) reported hospital mortality. The pooled results showed no significant difference between the therapy and control groups (OR: 1.17, 95% CI, 0.57 to 2.38). Four studies, including Du 2021, Zhang 2017, VanDerGeest 2014(27), and Albert 2014, reported 28-day mortality. The results showed no significant difference between the therapy and control groups (OR: 0.71, 95%) CI, 0.45 to 1.14). Three studies, Du 2021, VanDerGeest 2014, and Albert 2014, reported 90-day mortality. The results showed no significant difference between the therapy and control groups (OR: 0.76, 95% CI, 0.35 to 1.63). No indicator showed statistical significance with respect to mortality. (Figure 2) Figure 2 (A) Forest plot for ICU mortality; (B) Forest plot for hospital mortality; (C) Forest plot for 28-day mortality; (D) Forest plot for 90-day mortality Effect of antifungal therapy on pulmonary *Candida* colonization patients' ICU length of 3.4 stay

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2	152	Four studies, including Zhang 2017, Griffin2016, Ong 2013, and Nseir 2007, reported ICU length of
3	153	stay. The results indicated non-significant differences for ICU length of stay among patients
4	154	receiving antifungal treatment (SMD: -0.15, 95% CI, -0.88 to 0.59), as shown in Figure 3.
5		
6 7	155	Figure 3 Forest plot for ICU length of stay
8 9	156	3.5 Effect of antifungal therapy on pulmonary <i>Candida</i> colonization patients' MV duration
10	157	Three studies, including Zhang 2017, Griffin 2016, and Nseir 2007, reported the duration of MV. We
11	158	did not identify a significant difference between the therapy and control groups regarding MV
12	150	duration (SMD: 0.11, 0.5% CL = 0.88 to 1.10), as shown in Figure 4
13 14	139	duration (SMD: 0.11, 95/001, -0.88 to 1.10), as shown in Figure 4.
15	160	Figure 4 Forest plot for MV duration
16	100	i igure i i orest prot for fir v duration
17	161	3.6 Effect of antifungal therapy on VAP
18		
19	162	Six studies, including Du 2021, Zhang 2017, Griffin 2016, Lindau 2015, VanDerGeest 2014, and
20	163	Ong 2013, reported VAP. No significant difference was found between therapy and control groups
21	164	(OR: 1.54, 95% CI, 0.56 to 4.20), as shown in Figure 5.
22		
24	165	Figure 5 Forest plot for VAP
25		
26	166	3.7 Subgroup analysis
27	167	We conducted a subgroup analysis based on the offect of antifungal thereasy on VAD of the included
28	107	atudiog. The regult of the subgroup analysis based on the effect of antifungal inerapy on VAP of the included
29	100	studies. The result of the subgroup analysis indicate that the combined effect size is stable and
30	169	unaffected by different treatment types. As snown in Supplemental Figure 1.
32	170	Supplemental Figure 1 Forest plot for subgroup analysis of different treatment types
33	170	Supplemental Figure 1 Polest plot for subgroup analysis of unreferit treatment types
34	171	3.8 Sensitivity analysis and nublication bias
35	171	cio sensitivity unarysis una publication blas
36	172	A sensitivity analysis was performed by sequentially excluding one study at a time. This exclusion
3/ 20	173	did not significantly impact the results, with the pooled OR ranging from 1.00 (0.51-1.96) to 2.07
30	174	(0.74-5.78) (Supplemental Figure 2). Because only 9 related studies were included in this report,
40	175	approaches for detecting publication bias would have exhibited limited efficacy. Consequently, the
41	176	evaluation of publication bias was not conducted.
42		
43	177	Supplemental Figure 2 Sensitivity analysis for VAP
44	178	4 Discussion
45 46	170	
40	179	In this study, we observed that antifungal therapy administered to mechanically ventilated nations
48	180	with <i>Candida</i> colonization did not show a significant impact on patient outcomes, which were
49	181	measured by indicators including mortality hospital length of stay ICU length of stay mechanical
50	182	ventilation duration and incidence of VAP and the result is stable when taking different treatment
51	183	types into consideration. A study by Du declared that antifungal treatment was associated with a
52	184	reduced risk of VAP while an autonsy study involving 232 samples showed that although Candida is
53	194	2 common pathogen, the incidence of <i>Candida</i> provincing in ICU patients is extremely low(4, 11)
54 55	105	Inconsistent with the results of the previous studies, a mote analysis found that <i>Candida</i> nulmonory
55 56	100	adonization probably had noorar alinical outcomes owing to longer machenical ventilation duration
57	10/	bishor 28 day mortality, higher ICU mortality, and larger ICU largeth of stay(28). Eventhermore,
58	100	ingher 20-day mortanty, ingher 100 mortanty, and longer 100 length of stay(28). Furthermore, a
59		5
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- 189 study by Ioannou found that about half of the patients with *Candida* spp. isolation from their 190 respiratory secretions were treated with antifungals. Considering the factor that patients under more 191 critical condition could be treated with antifungals more often, a multivariate regression analysis was 192 conducted identifying antifungal use as an independent factor associated with total hospital 193 mortality(2). Without listing the specific articles for verification, the guideline strongly recommends
- mortality(2). Without listing the specific articles for verification, the guideline strongly recommends
   that *Candida* colonization rarely requires treatment with antifungal therapy(29). Our study, may help
- 9 195 to provide more information on this problem: whether *Candida* pulmonary colonization simply
- 10 196 symbolizes the severity of diseases or actually has influence on outcomes(30, 31).
   11

*Candida* colonization in the respiratory tract is related to higher inflammation and may accelerate the disease process(32, 33). A few studies used inhalation of antifungal drugs as therapy, which did not show significant influence on patients' outcomes. This may lead to direct inhibition or damage of the alveolar-capillary membrane, resulting in an influx of surfactant-inactivating plasma proteins(21, 27). After Candida colonization, current increases in antifungal drug resistance in Candida spp. and clinical treatment failures are of concern(34). Previous history of antifungal prescription influences Candida species distribution and susceptibility profile to antifungal agents(35). Inadequate dose and treatment failure may contribute to high mortality(36). 

Considering the various conditions, we thought that various factors cause poor clinical outcomes: antifungal treatment may have more harm than benefit in clinically ill patients. Different antifungal drugs can have varying sensitivities or resistances as well as potential toxicity or adverse effects. Inadequate dosing of antifungal drugs may also be a contributing factor. Although the analysis of this study showed that antifungal treatment did not improve patients' clinical outcomes, the sample size of included studies were limited and the 95% confidence intervals were wide. Further studies should be conducted to verify their influence. Considering retrospective and current studies can only provide hypotheses to support the existence of a correlation, a prospective randomized controlled trial might be a more appropriate solution to explore the effect of antifungal treatment on patients with respiratory *Candida* colonization in combination with mechanical ventilation. 

Based on the findings of this meta-analysis, the use of antifungal medication on mechanical-ventilated patients with respiratory Candida colonization does not appear to improve patients' clinical outcomes. No significant differences were observed in ICU mortality, hospital mortality, 28-day mortality, 90-day mortality, ICU length of stay, MV duration, and VAP associated with different treatment regimens. Further analysis of subgroups based on different treatment types confirmed these conclusions. Therefore, the use of antifungal medication is not recommended for the decolonization of mechanical-ventilated patients with respiratory Candida colonization. 

The strength of this study is that it included a number of outcome indicators to assess the effectiveness of antifungal treatment, with subgroup analyses performed based on the type of treatment administered. However it encountered several limitations. Most studies included are retrospective studies, raising potential concerns regarding their external validity. Additionally, some studies described the precise style, name, dose, and administration method of antifungal drugs, while others did not. Furthermore, this study is limited by the number of studies included, especially when it comes to single outcomes such as ICU mortality. Moreover, most studies included were cohort studies instead of random contral trials, which provide stronger evidence. 

- 230 5 Author Contributions

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**BMJ** Open HX and HY provided article ideas and completed a literature search. LL and SS contributed to the data analysis and manuscript writing. HX is the guarantor. **Conflict of Interest** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Patient consent for publication Not applicable. **Ethics** approval Not applicable. **Data Availability Statement** The raw data of this study can be obtained from corresponding author under reasonable request. Funding This study was funded by Changsha Municipal Health Committee (No.KJ-B2023032). Reference Pendleton KM, Huffnagle GB, Dickson RP. The significance of Candida in the human 1. respiratory tract: our evolving understanding. Pathog Dis. 2017;75(3). Ioannou P, Vouidaski A, Spernovasilis N, Alexopoulou C, Papazachariou A, Paraschou E, et 2. al. Candida spp. isolation from critically ill patients' respiratory tract. Does antifungal treatment affect survival? Germs. 2021;11(4):536-43. Charles MP, Easow JM, Joseph NM, Ravishankar M, Kumar S, Sivaraman U. Aetiological 3. agents of ventilator-associated pneumonia and its resistance pattern - a threat for treatment. Australas Med J. 2013;6(9):430-4. Du H, Wei L, Li W, Huang B, Liu Y, Ye X, et al. Effect of Nebulized Amphotericin B in 4. Critically ill Patients With Respiratory Candida spp. De-colonization: A Retrospective Analysis. Front Med (Lausanne). 2021;8:723904. Tehrani S, Saffarfar V, Hashemi A, Abolghasemi S. A Survey of Genotype and Resistance 5. Patterns of Ventilator-Associated Pneumonia Organisms in ICU Patients. Tanaffos. 2019;18(3):215-22. 6. Farag AM, Tawfick MM, Abozeed MY, Shaban EA, Abo-Shadi MA. Microbiological profile of ventilator-associated pneumonia among intensive care unit patients in tertiary Egyptian hospitals. J Infect Dev Ctries. 2020;14(2):153-61. Babaei S, Pourabdollah M, Aslanimehr M, Nikkhahi F, Mahmoodian S, Hasani Y, et al. 7. Frequency of Multi-Drug Resistance and Molecular Characteristics of Resistance to Colistin in Acinetobacter baumannii Collected from Patients in Intensive Care Units with Ventilator-Associated Pneumonia. Tanaffos. 2021;20(4):345-52. 

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Figure 1 Flowchart of studies identified, excluded, and included

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1 2 3 4 5	Supplemental	Table 2. Quality ass	sessment of inclu	ded studies				n-2024-083918 ( pyright, includi		
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### PRISMA 2020 Checklist

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1 2	PRIS	MA 2	020 Checklist	
3 4 5	Section and Topic	ltem #	Checklist item	Location where item is reported
6	TITLE			
7	Title	1	Identify the report as a systematic review. 5	L1
8	ABSTRACT	1		
9 10	Abstract	2	See the PRISMA 2020 for Abstracts checklist.	L75
11	INTRODUCTION			
12	Rationale	3	Describe the rationale for the review in the context of existing knowledge.	L55
13	B Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	L71
14	METHODS		te se	
15	Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	L90
17	, Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted by tudies. Specify the date when each source was last searched or consulted.	L76
10	Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	L81
20 21	Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how man device wers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	L85
22 23 24	Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of attomation tools used in the process.	L85
25 26	5 Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with end of outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	L109
27 28	, }	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	L108
29 30	Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	L113
31	Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	L121
32	Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study of terkention characteristics and comparing against the planned groups for each synthesis (item #5)).	L114
34 35 24		13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	L106
37	7	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	L120
38 39	3	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	L120
40	)	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analys 🖁, meta-regression).	L181
41		13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	L131
42	Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biase	L133
44	Certainty	15	Describe any methods used to assess reactainty (or repridence) in the body of revidence / or repridence / or r	L131



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### PRISMA 2020 Checklist

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PRIS	5MA 2	2020 Checklist	
Section and Topic	ltem #	Checklist item	Location where item is reported
assessment		ng on	
RESULTS		fo 22	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure1
0	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were kulled.	Figure1
Study characteristics	17	Cite each included study and present its characteristics.	Supplemental Table 1
4 Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplemental Table 2
6 Results of 7 individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an great estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure2-5
8 Results of 9 syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supplemental Table 2
<b>0</b> 1	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary sting ate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	L134
2	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
3	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	L186
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis as as as a based.	NA
6 Certainty of 7 evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
8 DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	L194
0	23b	Discuss any limitations of the evidence included in the review.	L36
2	23c	Discuss any limitations of the review processes used.	L36
3	23d	Discuss implications of the results for practice, policy, and future research.	L224
4 OTHER INFORMA	TION		
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	L34
o protocol	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
8	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
9 Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the regime.	L252
Competing interests	26	Declare any competing interests of review authors.	L240
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; date extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	L250
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#### Search:

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(ventilator-associated pneumonia OR VAP OR pneumonia, ventilator-associated OR ventilatorassociated pneumonia OR ventilator-acquired pneumonia OR mechanical ventilation) AND (Candida OR Candida spp OR Candida colonization OR Candida airway colonization)

#### **Details:**

("pneumonia, ventilator associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilatorassociated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "associated" [All Fields] AND "pneumonia" [All Fields]) OR "ventilator associated pneumonia" [All Fields] OR "VAP" [All Fields] OR (("pneumonia" [MeSH Terms] OR "pneumonia"[All Fields] OR "pneumonias"[All Fields] OR "pneumoniae"[All Fields] OR "pneumoniae s"[All Fields]) AND "ventilator-associated"[All Fields]) OR ("pneumonia, ventilator associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia" [All Fields] OR ("ventilator" [All Fields] AND "associated" [All Fields] AND "pneumonia" [All Fields]) OR "ventilator associated pneumonia" [All Fields]) OR ("pneumonia, ventilator associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator" [All Fields] AND "acquired" [All Fields] AND "pneumonia" [All Fields]) OR "ventilator acquired pneumonia" [All Fields]) OR ("respiration, artificial" [MeSH Terms] OR ("respiration" [All Fields] AND "artificial" [All Fields]) OR "artificial respiration" [All Fields] OR ("mechanical" [All Fields] AND "ventilation" [All Fields]) OR "mechanical ventilation" [All Fields])) AND ("candida" [MeSH Terms] OR "candida" [All Fields] OR "candidae" [All Fields] OR "candidas"[All Fields] OR (("candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]) AND ("sci public policy"[Journal] OR "spp"[All Fields])) OR (("candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]) AND ("colonisation" [All Fields] OR "colonisations" [All Fields] OR "colonise" [All Fields] OR "colonised" [All Fields] OR "coloniser" [All Fields] OR "colonisers" [All Fields] OR "colonises" [All Fields] OR "colonising" [All Fields] OR "colonization" [All Fields] OR "colonizations"[All Fields] OR "colonize"[All Fields] OR "colonized"[All Fields] OR "colonizer"[All Fields] OR "colonizers"[All Fields] OR "colonizes"[All Fields] OR "colonizing"[All Fields])) OR (("candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]) AND ("airway"[All Fields] OR "airway s"[All Fields] OR "airways"[All Fields]) AND ("colonisation"[All Fields] OR "colonisations"[All Fields] OR "colonise" [All Fields] OR "colonised" [All Fields] OR "coloniser" [All Fields] OR "colonisers"[All Fields] OR "colonises"[All Fields] OR "colonising"[All Fields] OR "colonization" [All Fields] OR "colonizations" [All Fields] OR "colonize" [All Fields] OR "colonized" [All Fields] OR "colonizer" [All Fields] OR "colonizers" [All Fields] OR "colonizes" [All Fields] OR "colonizing"[All Fields])))

#### **Translations:**

ventilator-associated pneumonia: "pneumonia, ventilator-associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "associated"[All Fields] AND "pneumonia"[All Fields]) OR "ventilator associated pneumonia"[All Fields]) OR "ventilator associated pneumonia"[All Fields]

Page 27 of 26

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# **BMJ Open**

#### Clinical outcomes of antifungal therapy on Candida pulmonary colonization in immunocompetent patients with invasive ventilation: A systematic review and meta-analysis

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<b>Primary Subject Heading</b> :	Intensive care
Secondary Subject Heading:	Evidence based practice
Keywords:	Meta-Analysis, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, Pulmonary Disease < Lung Diseases





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### Clinical outcomes of antifungal therapy on Candida pulmonary colonization in immunocompetent patients with invasive ventilation: A systematic review and meta-analysis

 Keywords: *Candida* colonization, pulmonary, antifungal therapy, mechanical ventilation, metaanalysis.

### 3 Abstract

**Objective:** This study aimed to use systematic review and meta-analysis to establish the 5 influence of antifungal therapy on pulmonary *Candida* colonization of patients with mechanical 6 ventilation.

**Design:** Systematic review and meta-analysis.

**Data sources:** An extensive search was undertaken on publications from inception to July 25,
2023, through PubMed, Web of Science, Medline, Embase, China National Knowledge
Infrastructure, Wanfang Data and VIP Databases.

Eligibility criteria for selecting studies: Randomized trials, cohort studies, and case-control
 studies comparing the efficacy of antifungal treatment in immunocompetent patients with pulmonary
 *Candida* colonization after invasive ventilation.

14 Data extraction and synthesis: Two reviewers independently extracted the data and assessed 15 the quality of studies. Dichotomous outcomes were expressed as odds ratios (OR) with 95% 16 confidence intervals (CIs). Continuous outcomes were expressed as standardized mean differences 17 (SMD) with 95% CIs.

Primary and secondary outcome measures: The primary outcomes included intensive care
 unit (ICU), hospital, 28-day, and 90-day mortality. The secondary outcomes included ICU length of
 stay, mechanical ventilation (MV) duration, and ventilator-associated pneumonia (VAP).

**Results:** Nine high-quality studies were included. According to the data collected from these nine studies, there is no significant evidence showing a difference between the therapy group treated with antifungal drugs and the control group without antifungal drugs in clinical outcomes, including intensive care unit mortality (OR: 1.37; 95% CI, 0.84 to 2.22), hospital mortality (OR: 1.17; 95% CI, 0.57 to 2.38), 28-day mortality (OR; 0.71, 95% CI, 0.45 to 1.14), 90-day mortality (OR; 0.76, 95% CI 0.35 to 1.63), intensive care unit length of stay (SMD: -0.15; 95% CI -0.88 to 0.59), mechanical ventilation duration (SMD: 0.11; 95%CI -0.88 to 1.10), and ventilator-associated pneumonia (OR: 1.54; 95% CI 0.56 to 4.20). Subgroup analysis of different treatment types indicates that the combined effect size is stable and unaffected by different treatment types including inhalation (OR: 2.32; 95% CI 0.30 to 18.09) and intravenous (OR: 0.65; 95% CI 0.13 to 3.34). 

Solution: The application of antifungal treatment did not improve clinical outcomes in patients with mechanical ventilation. We do not suggest initiating antifungal treatment in patients with *Candida* pulmonary colonization after invasive ventilation.

34 35	<b>Registration:</b> This study was registered in the International Prospective Register of Systematic Reviews, with the registration number CRD42020161138.
36	Strengths and limitations of this study:
37 38	1. This study included a number of outcome indicators to assess the effectiveness of antifungal treatment, with subgroup analyses performed based on the type of treatment administered.
39 40	2. Most studies included are retrospective studies, raising potential concerns regarding their external validity.
41 42	3. Some studies described the precise style, name, dose, and administration method of antifungal drugs, while others did not.
43 44	4. This study is limited by the number of studies included, especially when it comes to single outcomes such as ICU mortality.
45 46	5. Most studies included were cohort studies instead of random contral trials, which provide stronger evidence.
47	1 Introduction
48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65	<i>Candida</i> frequently exists in the normal oral cavity, upper respiratory tract, lower-intestinal tract and vagina[1]. In tracheal aspirates from patients with mechanical ventilation (MV), 30% have <i>Candida</i> isolation, and nearly 50% from patients suspected to have a ventilator-associated pneumonia (VAP)[2, 3]. When respiratory <i>Candida</i> colonization is detected, it is difficult to differentiate between relatively harmless colonization and invasive infection, and leads to a therapeutic dilemma[4]. Although few studies reported limited attributable intensive care unit (ICU) mortality of VAP, the death rate related to VAP cannot be denied according to the majority of previous studies[5-8]. The incidence of VAP frequently extends hospital stay, elevates the economic burden, and raises the mortality rate[9]. The presence of <i>Candida</i> in respiratory samples is defined as <i>Candida</i> colonization instead of infection because the appearance of <i>Candida</i> pneumonia is rare[10-13]. For several years, arguments have arisen about whether <i>Candida</i> colonization negatively affects or simply indicates disease severity or immunosuppression in critically ill patients[14-16]. We found that the outcomes of antifungal treatment for <i>Candida</i> colonization in pulmonary tract among different studies were controversial, as some studies found that antifungal treatment was associated with lower mortality, some found that treatment made no difference in mortality, while others found that it prolonged MV duration, ICU length of stay, and hospital length of stay[10, 11, 17, 18]. Therefore, we performed a systematic review and meta-analysis to establish the influence of antifungal treatment on pulmonary <i>Candida</i> colonization.
66	2 Method
67	2.1 Information sources and search strategy

This study followed the Preferred Reporting Items for Systematic Review and Meta-Analysis criteria for systematic reviews and meta-analyzes[19]. An extensive search was undertaken on publications from inception to July 25, 2023, through PubMed, Web of Science, Medline, Embase, China National Knowledge Infrastructure, Wanfang Data and VIP Databases. The searching syntax included the following Medical Subject Headings (MeSH) and text words which are varied 

individually according to different databases: ventilator-associated pneumonia, *Candida*. We used the
following search strategies in all of the databases above: (ventilator-associated pneumonia OR VAP
OR pneumonia, ventilator-associated OR ventilator-associated pneumonia OR ventilator-acquired
pneumonia OR mechanical ventilation) AND (*Candida* OR *Candida* spp OR *Candida* colonization
OR *Candida* airway colonization). There were no language restrictions on studies searching. The
listed references of relevant studies were also evaluated to enlarge the search scope and ensure a
complete search. Full search strategy of pubmed database is provided in the supplemental material.

- 80 Selection process of the article was performed by two researchers (LL and SS) independently. The
   81 titles and abstracts of the entries identified in the search were screened. Full text version of all articles
- $\frac{12}{13}$  82 that potentially met the eligibility criteria was reviewed to make a decision. Disagreements, if any,
- $^{13}_{14}$  83 were resolved through discussion with a third researcher (HX).

### 15 16 84 2.2 Inclusion criteria

Randomized trials, cohort studies, and case-control studies were included while selecting. In the included studies, the patients were adults (>18 years old) who were diagnosed with pulmonary Candida colonization after invasive ventilation. Pulmonary Candida colonization was defined as the presence of *Candida* in bronchoalveolar lavage samples, endotracheal aspiration samples, protected brush specimens, or any positive airway secretion specimens. 

### <sup>24</sup><sub>25</sub> 90 **2.3 Exclusion criteria**

We excluded case reports and studies on pregnant, immunocompromised patients, or those who received antifungal treatment for reasons other than *Candida* colonization. Patients with candidemia or invasive candidiasis were also excluded, and the diagnostic criteria were positive results of direct detection, in which blood or tissue specimens were cultured, or indirect detection, in which surrogate markers and polymerase chain reaction assays were used[20]. 

### 96 2.4 Data collection

We screened titles and abstracts, reviewed the full text, and extracted data using an Excel sheet (Microsoft Corporation). We primarily collected the characteristics of title, author, journal, year, type, participants, inclusion or exclusion criteria, interventions, and clinical outcomes. Clinical outcomes included 28-day mortality, 90-day mortality, ICU mortality, hospital mortality, ICU length of stay, MV duration, and VAP. Disagreements were resolved by discussion with a third reviewer if necessary. 

## <sup>43</sup> 103 **2.5 Quality assessment**

We used the Cochrane risk assessment tool to measure the risk of randomized controlled trials and
 the Newcastle-Ottawa Scale to measure the quality of cohort and case-control studies[21]. Studies
 that scored at least six points were regarded as high-quality and included.

<sup>49</sup><sub>50</sub> 107 **2.6 Patient and public involvement** 

<sup>51</sup> 108 Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination
 <sup>52</sup> 109 plans of this research.

## 5455 110 2.7 Statistical analysis

#### **BMJ** Open

BMJ Open: first published as 10.1136/bmjopen-2024-083918 on 22 October 2024. Downloaded from http://bmjopen.bmj.com/ on June 7, 2025 at Agence Bibliographique de Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies. Statistical analysis was performed by Stata software (Version 16.0). Dichotomous outcomes such as VAP, ICU mortality, hospital mortality, 28-day mortality, and 90-day mortality, were expressed as odds ratios (OR) with 95% confidence intervals (CIs). Continuous outcomes (ICU length of stay and MV duration) were expressed as standardized mean differences (SMD) with 95% CIs. We analyzed the data using the Inverse-Variance method with the fixed-effect model if there was no obvious heterogeneity (P > 0.1), or else random-effect model if the heterogeneity was significant (P < 0.1). Moreover, heterogeneity was quantified using the  $I^2$  test. The interpretation of  $I^2$  was guided by the Cochrane Handbook for Systematic Reviews of interventions (Version 5.2.0, updated June 2017). Sensitivity analyses was conducted by excluding one study at a time from the analysis to assess the stability of the results. Subgroup analyses were performed on the effect of antifungal therapy. Publication bias was not assessed since there were fewer than 10 studies in this meta-analysis. Results **Study selection** 3.1 In total, 2947 records were identified. With 1246 duplicates removed and 1670 irrelevant records excluded, we assessed 31 studies for eligibility, of which 9 were included. 22 studies were excluded because of the lack of antifungal treatment, lack of supporting experimental data, lack of detection of pulmonary secretion, and occurrence in a special population (Figure 1). All patients received MV, had at least one positive culture of *Candida* in the pulmonary tract, and received different antifungal treatments. Figure 1 Flowchart of studies identified, excluded, and included 3.2 Study characteristics and quality assessment Of the nine articles included in the study, seven were retrospective cohort studies, one case-control 

study, and one randomized clinical trial. Two studies were conducted in North America, five in Europe, and two in Asia, giving the studies a wide geographical coverage. Other characteristics of the included studies are summarized in Supplemental Table 1, including years of accuracy, location, study design, population, number of patients, outcomes, *Candida* colonization and antifungal treatment. The columns of the quality assessment list and their corresponding points are listed in Supplemental Table 2. All included studies were assessed to be of high quality. 

#### Effect of antifungal therapy on pulmonary *Candida* colonization patients' mortality 3.3

Three studies, including Ioannou 2021[2], Ong 2013[22], and Nseir 2007[23] reported ICU mortality. We found no significant difference between the therapy and control groups (OR: 1.37, 95% CI, 0.84 to 2.22). Six studies, including Du 2021[4], Ioannou 2021, Zhang 2017[24], Griffin 2016[25], Lindau 2015[26], and Albert 2014[27] reported hospital mortality. The pooled results showed no significant difference between the therapy and control groups (OR: 1.17, 95% CI, 0.57 to 2.38). Four studies, including Du 2021, Zhang 2017, VanDerGeest 2014[28], and Albert 2014, reported 28-day mortality. The results showed no significant difference between the therapy and control groups (OR: 0.71, 95%) CI, 0.45 to 1.14). Three studies, Du 2021, VanDerGeest 2014, and Albert 2014, reported 90-day mortality. The results showed no significant difference between the therapy and control groups (OR: 0.76, 95% CI, 0.35 to 1.63). No indicator showed statistical significance with respect to mortality. (Figure 2) 

2 3 4	151 152	Figure 2 (A) Forest plot for ICU mortality; (B) Forest plot for hospital mortality; (C) Forest plot for 28-day mortality; (D) Forest plot for 90-day mortality
5 6 7	153 154	<b>3.4</b> Effect of antifungal therapy on pulmonary <i>Candida</i> colonization patients' ICU length of stay
8 9 10 11	155 156 157	Four studies, including Zhang 2017, Griffin2016, Ong 2013, and Nseir 2007, reported ICU length of stay. The results indicated non-significant differences for ICU length of stay among patients receiving antifungal treatment (SMD: -0.15, 95% CI, -0.88 to 0.59), as shown in Figure 3.
12 13	158	Figure 3 Forest plot for ICU length of stay
14 15 16	159	3.5 Effect of antifungal therapy on pulmonary <i>Candida</i> colonization patients' MV duration
17 18 19 20	160 161 162	Three studies, including Zhang 2017, Griffin 2016, and Nseir 2007, reported the duration of MV. We did not identify a significant difference between the therapy and control groups regarding MV duration (SMD: 0.11, 95%CI, -0.88 to 1.10), as shown in Figure 4.
21 22	163	Figure 4 Forest plot for MV duration
23 24	164	3.6 Effect of antifungal therapy on VAP
25 26 27 28 20	165 166 167	Six studies, including Du 2021, Zhang 2017, Griffin 2016, Lindau 2015, VanDerGeest 2014, and Ong 2013, reported VAP. No significant difference was found between therapy and control groups (OR: 1.54, 95% CI, 0.56 to 4.20), as shown in Figure 5.
29 30 31	168	Figure 5 Forest plot for VAP
32 32	169	3.7 Subgroup analysis
34 35 36 37	170 171 172	We conducted a subgroup analysis based on the effect of antifungal therapy on VAP of the included studies. The result of the subgroup analysis indicate that the combined effect size is stable and unaffected by different treatment types. As shown in Supplemental Figure 1.
38 39	173	Supplemental Figure 1 Forest plot for subgroup analysis of different treatment types
40 41	174	3.8 Sensitivity analysis and publication bias
42 43 44 45 46 47 48	175 176 177 178 179	A sensitivity analysis was performed by sequentially excluding one study at a time. This exclusion did not significantly impact the results, with the pooled OR ranging from 1.00 (0.51-1.96) to 2.07 (0.74-5.78) (Supplemental Figure 2). Because only 9 related studies were included in this report, approaches for detecting publication bias would have exhibited limited efficacy. Consequently, the evaluation of publication bias was not conducted.
49 50	180	Supplemental Figure 2 Sensitivity analysis for VAP
51 52	181	4 Discussion
53 54 55 56 57 58	182 183 184 185	In this study, we observed that antifungal therapy administered to mechanically ventilated patients with <i>Candida</i> colonization did not show a significant impact on patient outcomes, which were measured by indicators including mortality, hospital length of stay, ICU length of stay, mechanical ventilation duration, and incidence of VAP, and the result is stable when taking different treatment
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types into consideration. A study by Du declared that antifungal treatment was associated with a reduced risk of VAP, while an autopsy study involving 232 samples showed that although *Candida* is a common pathogen, the incidence of *Candida* pneumonia in ICU patients is extremely low[4, 11]. Inconsistent with the results of the previous studies, a meta-analysis found that *Candida* pulmonary colonization probably had poorer clinical outcomes owing to longer mechanical ventilation duration, higher 28-day mortality, higher ICU mortality, and longer ICU length of stay[29]. Furthermore, a study by Ioannou found that about half of the patients with *Candida* spp. isolation from their respiratory secretions were treated with antifungals. Considering the factor that patients under more critical condition could be treated with antifungals more often, a multivariate regression analysis was conducted identifying antifungal use as an independent factor associated with total hospital mortality[2]. Without listing the specific articles for verification, the guideline strongly recommends that *Candida* colonization rarely requires treatment with antifungal therapy[30]. Our study, may help to provide more information on this problem: whether *Candida* pulmonary colonization simply symbolizes the severity of diseases or actually has influence on outcomes[31, 32]. Candida colonization in the respiratory tract is related to higher inflammation and may accelerate the disease process[33, 34]. A few studies used inhalation of antifungal drugs as therapy, which did not

show significant influence on patients' outcomes. This may lead to direct inhibition or damage of the alveolar-capillary membrane, resulting in an influx of surfactant-inactivating plasma proteins [22, 28]. After *Candida* colonization, current increases in antifungal drug resistance in *Candida* spp. and clinical treatment failures are of concern[35]. Previous history of antifungal prescription influences *Candida* species distribution and susceptibility profile to antifungal agents[36]. Inadequate dose and treatment failure may contribute to high mortality[37]. 

Considering the various conditions, we thought that various factors cause poor clinical outcomes: antifungal treatment may have more harm than benefit in clinically ill patients. Different antifungal drugs can have varying sensitivities or resistances as well as potential toxicity or adverse effects. Inadequate dosing of antifungal drugs may also be a contributing factor. Although the analysis of this study showed that antifungal treatment did not improve patients' clinical outcomes, the sample size of included studies were limited and the 95% confidence intervals were wide. Further studies should be conducted to verify their influence. Considering retrospective and current studies can only provide hypotheses to support the existence of a correlation, a prospective randomized controlled trial might be a more appropriate solution to explore the effect of antifungal treatment on patients with respiratory *Candida* colonization in combination with mechanical ventilation. 

Based on the findings of this meta-analysis, the use of antifungal medication on mechanical-ventilated patients with respiratory Candida colonization does not appear to improve patients' clinical outcomes. No significant differences were observed in ICU mortality, hospital mortality, 28-day mortality, 90-day mortality, ICU length of stay, MV duration, and VAP associated with different treatment regimens. Further analysis of subgroups based on different treatment types confirmed these conclusions. Therefore, the use of antifungal medication is not recommended for the decolonization of mechanical-ventilated patients with respiratory Candida colonization. 

The strength of this study is that it included a number of outcome indicators to assess the effectiveness of antifungal treatment, with subgroup analyses performed based on the type of treatment administered. However it encountered several limitations. Most studies included are retrospective studies, raising potential concerns regarding their external validity. Additionally, some studies described the precise style, name, dose, and administration method of antifungal drugs, while others did not. Furthermore, this study is limited by the number of studies included, especially when 

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- it comes to single outcomes such as ICU mortality. Moreover, most studies included were cohort
   studies instead of random contral trials, which provide stronger evidence.
   Author Contributions
  - 233 **5** Author Contributions
- <sup>7</sup> 234 HX and HY provided article ideas and completed a literature search. LL and SS contributed to the data analysis and manuscript writing. HX is the guarantor.
- 10112366Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial
relationships that could be construed as a potential conflict of interest.

- 239 7 Patient consent for publication
- <sup>18</sup> 240 Not applicable.

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- <sup>20</sup><sub>21</sub> 241 **8 Ethics approval**
- <sup>22</sup><sub>23</sub> 242 Not applicable.
- 2425243**9Data Availability Statement**
- The raw data of this study can be obtained from corresponding author under reasonable request.
- 29 245 **10 Funding** 30
- This study was funded by Changsha Municipal Health Committee (No.KJ-B2023032).
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#### BMJ Open

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<ul> <li>35</li> <li>36</li> <li>37</li> <li>38</li> <li>39</li> <li>40</li> <li>41</li> <li>42</li> <li>43</li> <li>44</li> <li>45</li> <li>46</li> <li>47</li> <li>48</li> <li>49</li> <li>50</li> <li>51</li> </ul>	289 290 291	13.	Azoulay E, Timsit JF, Tafflet M, de Lassence A, Darmon M, Zahar JR, Adrie C, Garrouste- Orgeas M, Cohen Y, Mourvillier B <i>et al</i> : <b>Candida colonization of the respiratory tract and</b> <b>subsequent pseudomonas ventilator-associated pneumonia</b> . <i>Chest</i> 2006, <b>129</b> (1):110-117.
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Figure 1 Flowchart of studies identified, excluded, and included

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1 2 3 4 5	Supplemental Table 2. Quality assessment of included studies											
6 7 8	Cohort study (Newcastle-Ottawa scale)											
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		Representativeness of exposed cohort	Selection of the non- exposed cohort	Ascertainment of exposure	outcome of interest	Assessment of outcome	Follow- up duration	ated to text and been and been and been and been and been and been	bility of cohorts	Total score		
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# PRISMA 2020 Checklist

Page 23 of 26			BMJ Open Ged B	
1 2	PRIS	MA 2	020 Checklist	
3 4 5	Section and Topic	ltem #	Checklist item	Location where item is reported
6	TITLE			
7	Title	1	Identify the report as a systematic review.	L1
8	ABSTRACT			
9	Abstract	2	See the PRISMA 2020 for Abstracts checklist.	L75
11	INTRODUCTION			
12	Rationale	3	Describe the rationale for the review in the context of existing knowledge.	L55
13	B Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	L71
14	METHODS	1	text of the second	
15	Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	L90
16	, Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted by tudies. Specify the date when each source was last searched or consulted.	L76
10	Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	L81
20 21	Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how man device wers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	L85
22 23 24 25 26	Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of attomation tools used in the process.	L85
	5 Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with end of outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	L109
27 28	, }	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	L108
29 30	Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	L113
31	Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	L121
32 33	Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study of terkention characteristics and comparing against the planned groups for each synthesis (item #5)).	L114
34 35 24		13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	L106
37	7	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	L120
38	3	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	L120
40	)	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analys 🖁, meta-regression).	L181
41		13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	L131
42	Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biase	L133
44	Certainty	15	Describe any methods used to assess reactainty (or repridence) in the body of revidence / or repridence / or r	L131

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# PRISMA 2020 Checklist

		BMJ Open	Page 24 of
PRIS	5MA 2	2020 Checklist	
Section and Topic	ltem #	Checklist item	Location where item is reported
assessment			
RESULTS		fo 22	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure1
0	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were known were known and the state of	Figure1
2 Study characteristics	17	Cite each included study and present its characteristics.	Supplemental Table 1
4 Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplemental Table 2
6 Results of 7 individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an great estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure2-5
8 Results of 9 syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supplemental Table 2
<b>0</b> 1	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary sting ate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	L134
2	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
3	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	L186
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis as to be a set of the	NA
6 Certainty of 7 evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
8 DISCUSSION	T		
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	L194
0	23b	Discuss any limitations of the evidence included in the review.	L36
2	23c	Discuss any limitations of the review processes used.	L36
3	23d	Discuss implications of the results for practice, policy, and future research.	L224
4 OTHER INFORMA	TION		
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	L34
o protocol	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
1 8	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
9 Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	L252
Competing interests	26	Declare any competing interests of review authors.	L240
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; date extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	L250
.5 •6		For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtmi	

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#### Search:

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(ventilator-associated pneumonia OR VAP OR pneumonia, ventilator-associated OR ventilatorassociated pneumonia OR ventilator-acquired pneumonia OR mechanical ventilation) AND (Candida OR Candida spp OR Candida colonization OR Candida airway colonization)

### **Details:**

("pneumonia, ventilator associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilatorassociated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "associated" [All Fields] AND "pneumonia" [All Fields]) OR "ventilator associated pneumonia" [All Fields] OR "VAP" [All Fields] OR (("pneumonia" [MeSH Terms] OR "pneumonia"[All Fields] OR "pneumonias"[All Fields] OR "pneumoniae"[All Fields] OR "pneumoniae s"[All Fields]) AND "ventilator-associated"[All Fields]) OR ("pneumonia, ventilator associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia" [All Fields] OR ("ventilator" [All Fields] AND "associated" [All Fields] AND "pneumonia" [All Fields]) OR "ventilator associated pneumonia" [All Fields]) OR ("pneumonia, ventilator associated" [MeSH Terms] OR ("pneumonia" [All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator" [All Fields] AND "acquired" [All Fields] AND "pneumonia" [All Fields]) OR "ventilator acquired pneumonia" [All Fields]) OR ("respiration, artificial" [MeSH Terms] OR ("respiration" [All Fields] AND "artificial" [All Fields]) OR "artificial respiration" [All Fields] OR ("mechanical" [All Fields] AND "ventilation" [All Fields]) OR "mechanical ventilation" [All Fields])) AND ("candida" [MeSH Terms] OR "candida" [All Fields] OR "candidae" [All Fields] OR "candidas"[All Fields] OR (("candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]) AND ("sci public policy"[Journal] OR "spp"[All Fields])) OR (("candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]) AND ("colonisation" [All Fields] OR "colonisations" [All Fields] OR "colonise" [All Fields] OR "colonised" [All Fields] OR "coloniser" [All Fields] OR "colonisers" [All Fields] OR "colonises" [All Fields] OR "colonising" [All Fields] OR "colonization" [All Fields] OR "colonizations"[All Fields] OR "colonize"[All Fields] OR "colonized"[All Fields] OR "colonizer"[All Fields] OR "colonizers"[All Fields] OR "colonizes"[All Fields] OR "colonizing"[All Fields])) OR (("candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR "candidas"[All Fields]) AND ("airway"[All Fields] OR "airway s"[All Fields] OR "airways"[All Fields]) AND ("colonisation"[All Fields] OR "colonisations"[All Fields] OR "colonise" [All Fields] OR "colonised" [All Fields] OR "coloniser" [All Fields] OR "colonisers"[All Fields] OR "colonises"[All Fields] OR "colonising"[All Fields] OR "colonization" [All Fields] OR "colonizations" [All Fields] OR "colonize" [All Fields] OR "colonized" [All Fields] OR "colonizer" [All Fields] OR "colonizers" [All Fields] OR "colonizes" [All Fields] OR "colonizing"[All Fields])))

### **Translations:**

ventilator-associated pneumonia: "pneumonia, ventilator-associated"[MeSH Terms] OR ("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "associated"[All Fields] AND "pneumonia"[All Fields]) OR "ventilator associated pneumonia"[All Fields]) OR "ventilator associated pneumonia"[All Fields]

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3	pneumonia: "pneumonia"[MeSH Terms] OR "pneumonia"[All Fields] OR "pneumonias"[All Fields]
4	OR "pneumoniae"[All Fields] OR "pneumoniae's"[All Fields]
5	ventilater accordented maximum ("maximum in ventilater accordinted"[MaSH Terms] OD
7	ventualor-associated pileunionia. pileunionia, ventualor-associated [westi fermis] OK
7 8	("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated
9	pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "associated"[All Fields] AND
10	"pneumonia"[All Fields]) OR "ventilator associated pneumonia"[All Fields]
11	ventilator acquired preumonia: "preumonia ventilator associated"[MeSH Terms] OP
12	ventulator-acquired pheumonia, pheumonia, ventulator-associated [westi remis] OK
13	("pneumonia"[All Fields] AND "ventilator-associated"[All Fields]) OR "ventilator-associated
14	pneumonia"[All Fields] OR ("ventilator"[All Fields] AND "acquired"[All Fields] AND
15	"pneumonia"[All Fields]) OR "ventilator acquired pneumonia"[All Fields]
16	mechanical ventilation: "respiration artificial"[MeSH Terms] OR ("respiration"[All Fields] AND
17	"artificial" [All Fields] OD "artificial regrination" [All Fields] OD ("masherical" [All Fields] AND
18	"aruncial" [All Fields]) OR "aruncial respiration" [All Fields] OR ("mechanical" [All Fields] AND
19	"ventilation"[All Fields]) OR "mechanical ventilation"[All Fields]
20	Candida: "candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR
21	"candidas"[All Fields]
22	Candida: "candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR
23	
25	"candidas"[All Fields]
26	spp: "Sci Public Policy"[Journal:jid0417663] OR "spp"[All Fields]
27	Candida: "candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR
28	"candidas"[All Fields]
29	colonization: "colonisation"[All Fields] OR "colonisations"[All Fields] OR "colonise"[All Fields]
30	OR "aplanizad"[All Fields] OR "aplanizar"[All Fields] OR "aplanizars"[All Fields] OR
31	OK colonised [All Fleids] OK colonisel [All Fleids] OK colonisels [All Fleids] OK
32	"colonises"[All Fields] OR "colonising"[All Fields] OR "colonization"[All Fields] OR
33	"colonizations"[All Fields] OR "colonize"[All Fields] OR "colonized"[All Fields] OR
34	"colonizer"[All Fields] OR "colonizers"[All Fields] OR "colonizes"[All Fields] OR
36	"colonizing"[All Fields]
37	Candida: "candida"[MeSH Terms] OR "candida"[All Fields] OR "candidae"[All Fields] OR
38	
39	"candidas"[All Fields]
40	airway: "airway"[All Fields] OR "airway's"[All Fields] OR "airways"[All Fields]
41	colonization: "colonisation"[All Fields] OR "colonisations"[All Fields] OR "colonise"[All Fields]
42	OR "colonised"[All Fields] OR "coloniser"[All Fields] OR "colonisers"[All Fields] OR
43	"colonises"[All Fields] OR "colonising"[All Fields] OR "colonization"[All Fields] OR
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45	"colonizations"[All Fields] OR "colonize"[All Fields] OR "colonized"[All Fields] OR
40	"colonizer"[All Fields] OR "colonizers"[All Fields] OR "colonizes"[All Fields] OR
47	"colonizing"[All Fields]
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