PRESENCE OF FUNGAL AGENTS IN HEALTHCARE WORKERS THAT PRACTICE HANDWASHING: A SYSTEMATIC REVIEW AND METAANALYSIS

PRESENCIA DE AGENTES FÚNGICOS EN TRABAJADORES DE LA SALUD QUE PRACTICAN EL LAVADO DE MANOS: REVISIÓN SISTEMÁTICA Y METAANÁLISIS

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Abstract

This study highlights the fungal agents present on healthcare workers hands. Through Proquest, ScienceDirect, Scielo, Pubmed and Springer were reviewed to summarize contributions of the past 10 years. A statistical analysis was performed to assess the risk ratio (RR) that fungal agents represent on healthcare personnel. The hands of healthcare workers are colonized by mycelial fungi and yeasts such as (*S. cerevisae, P. chrysogenum, Aspergillus niger, Aspergillus flavus, Rhodotorula spp., and Malassezia furfur*), for the case of this investigation the wide presence of *Candida spp* was observed (*C. parapsilosis sensu stricto, C. metapsilosis, C. orthopsilosis, C. albicans, C. famata, C. lusitaniae, C. krusei, C. kefyr, C. tropicalis, C. glabrata and C. guilliermondii*). Although the presence of fungi on healthcare workers hands was lower RR= 0.32, [0.17 to 0.60]; specifically, on physicians RR = 0.16 [95% CI 0.08, 0.31] and nurses RR = 0.08 [0.05, 0.13], the use of rings does represent a risk, as it is a vector to host fungi RR = 3.33 [2.16, 5.13]. Although health workers follow protocols for adequate handwashing before and after having contact with patients, presence of fungal agents on hands is evident. Inadequate hand hygiene by healthcare personnel can be reflected in microorganisms spreading and skin or urinary tract infections, septicemia and even patient's death.

Keywords: Hand, Healthcare workers, Fungi, Yeast, *Candida* spp.

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Resumen

Este estudio destaca los agentes fúngicos presentes en las manos de los trabajadores sanitarios. Por medio de Proquest, ScienceDirect, Scielo, Pubmed y Springer fueron revisadas para resumir las contribuciones de los últimos 10 años. Se realizó un análisis estadístico para evaluar la razón de riesgo (RR) que representan los agentes fúngicos en el personal de salud. Las manos de los trabajadores sanitarios están colonizadas por hongos miceliares y levaduras como (*S. cerevisae, P. chrysogenum, Aspergillus niger, Aspergillus flavus, Rhodotorula spp. Y Malassezia furfur*), para el caso de esta investigación se observó la amplia presencia de *Candida* spp. (*C. parapsilosis sensu stricto, C. metapsilosis, C. orthopsilosis, C. albicans, C. famata, C. lusitaniae, C. krusei, C. kefyr, C. tropicalis, C. glabrata y C. guilliermondii*). Aunque la presencia de hongos en las manos de los trabajadores de la salud fue menor RR = 0,32, [0,17 a 0,60]; específicamente, en médicos RR = 0,16 [0,08, 0,31] y enfermeras RR = 0,08 [0,05, 0,13], el uso de anillos sí representa un riesgo, ya que es un vector para hospedar hongos RR = 3,33 [2,16; 5,13]. Si bien los trabajadores de la salud siguen protocolos para un adecuado lavado de manos antes y después de tener contacto con los pacientes, es evidente la presencia de agentes fúngicos en las manos. La higiene inadecuada de manos, por parte del personal sanitario, puede reflejarse en la propagación de microorganismos e infecciones de la piel o del tracto urinario, septicemia e inclusive la muerte del paciente.

Palabras clave: Mano, Trabajadores sanitarios, Hongos, Levaduras, *Candida* spp.

Introduction

Healthcare-Associated Infections (HAIs), also known as "nosocomial" or "hospital" infections, are infections that patients acquire when they receive medical care in a hospital or health care facility (Haque et al. 2018). According to Scully et al., the most common HAIs are urinary tract infections, wound infections (after surgery), skin infections, and infections that cause vomiting and/or diarrhea (Scully 2014). In accordance with a World Health Organization (WHO) report, surgical site infection (SSI) is the most studied and frequent type of infection in low- and middle-income countries with incidence rates ranging between 1.2 and 23.6 per 100 surgical procedures and a combined incidence of 11.8%; in contrast, SSI rates vary between 1.2% and 5.2% in developed countries (World Health Organization 2011). In the reports presented by the National Institute of Health of Colombia, it was evidenced that, between 2015 and 2016, an average of 6474 infections associated with the use of devices were reported in intensive care units (ICU). The infections that were associated were bloodstream catheter (2680 cases), urinary tract catheter (1955 cases) and pneumonia associated with mechanical ventilation (1839 cases) (Gaviria et al. 2018). Additionally, in the study carried out by Ortiz-Mayorga et al., the costs of HAIs for the health system in a Colombian hospital were analyzed, being pneumonia associated with mechanical ventilation the one that represented the highest costs, followed by infections in the bloodstream, and finally, urinary infections (Ortiz-Mayorga et al. 2019).

HAIs that may occur in health systems are reflected in the appearance of either bacteria or fungi. Several persistent nosocomial pathogens in the environment persist for several hours, days or months on healthcare worker hands (HCW-H) (Dancer 2014; Sood and Perl 2016), with endospores that generally persist longer than vegetative bacteria (Suleyman, Alangaden, and Bardossy 2018). For instance, the presence of bacteria on dry surfaces such as *Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter spp.* (Otter et al. 2013) *Enterococcus spp., Clostridium difficile* (Chemaly et al. 2014), *E. coli* (Hübner et al. 2011), *Klebsiella spp., Serratia marcescens, Acinetobacter spp.* (Kramer, Schwebke, and Kampf 2006) and Norovirus (Kok 2014). In a study carried out by the Ministry of Health and Social Protection of Colombia, it was shown that isolates from blood samples in ICU corresponded to *K. pneumoniae* (12%),

S. aureus (10.7%) and *E. coli* (5.4 %), while isolates from non-ICU services corresponded to *S. aureus* (13.4%), *E. coli* (12.9%) and *K. pneumoniae* (8.7%). On the other hand, isolates from urine samples in ICU corresponded to *E. coli* (33.1%) and *K. pneumoniae* (15.3%), while isolates from non-ICU services corresponded to *E. coli* (4%) and *K. pneumoniae* (11%) (Gaviria et al. 2018; Ministerio de Salud y Protección Social 2012). Given that bacteria have a high presence in hospitals and medical centers, it is relevant to mention that fungi also represent a burden for health systems. Fungal infections of nosocomial origin have been categorized within the infections with highest increase worldwide, as well as Invasive Fungal Infections (IFI), which are associated with the increase in morbidity and mortality rates given their difficulty of early diagnosis (Pemána and Salavert 2013). In fact, the species as *Aspergillus* are the main cause of IFI due to molds in patients with hematopoietic progenitor and solid organ transplant recipients, followed by other molds considered emerging such as *Fusarium spp.*, *Scedosporium spp.* or Mucorales (Neofytos et al. 2010). Fungal infections, in particular, *Candida* spp. are responsible of 9 and 12% of all bloodstream infections (Timsit et al. 2015). For example, Leon et al., described that a high proportion of patients hospitalized in ICU were colonized with *Candida* spp. species, but only from 5 to 30% developed invasive candidiasis (León, Ostrosky-Zeichner, and Schuster 2014). In the study developed by Lortholary et al., incident episodes of candidemia were evidenced, where *C. albicans* (56%), *C. glabrata* (18.6%), *C. parapsilosis* (11.5%), *C. tropicalis* (9.3%), *C. krusei* (2.9%) and *C. kefyr* (1.8%), were the spices of *Candida spp.* isolated from hospitals (Lortholary et al. 2014). Regarding health workers, a study showed that yeasts *C. albicans, C. parapsilosis, C. glabrata, C. tropicali*s and *C. krusei* were presented on HCW-H (Sakita et al. 2017). At national level, Cortes et al., evidenced the distribution of *Candida* spp. species in patients with bloodstream infections, showing that *C. albicans, C. tropicalis, C. parapsilosis, C. glabrata* and *C. krusei* were the fungi found. The same study mentioned that between 37% and 45% of patients who have been affected by candidemia were hospitalized in ICU; in addition, cancer was the risk factor that triggered fungal infections in patients (Cortés et al. 2020).

Different antibiotics such as amphotericin B, fluconazole, micafungin, among other antifungal drugs have been used for clinical treatment of fungal infections; however, fungi in prolonged infections are not eliminated, resulting in serious antifungal resistance problems (Wang et al. 2018). For instance, it has been shown that yeasts such as *C. glabrata, C. krusei* and *C. auris* have generated resistance to drugs such as Fluconazole, voriconazole and posaconazole; while fungi such as *Cryptococcus spp.*, and *Fusarium spp.* presented high resistance to antibiotics such as Caspofungin, micafungin and anidulafungin; finally, organisms such as *C. auris* and *Aspergillus terreus* have developed intrinsic resistance to drugs such as Amphotericin B (Berman and Krysan 2020). Overall, emergence of multi-drug resistant *C. auris* and *C. glabrata* and the acquisition of invasive infections due to *C. parapsilosis, C. tropicalis* and *Aspergillus spp.* resistant to azoles, represent a serious threat to health considering the limited number of systematic antifungals available to treat IFI (Arastehfar et al. 2020). Since a great effort is made to combat the presence and spread of fungi, it is relevant to mention other preventive alternatives to avoid the appearance of fungi such as use of personal protection elements, cleaning, disinfection and continuous sterilization of spaces and instruments and hand hygiene (Escandón, Duarte, and Rivera 2010). It is estimated that HAIs occur because healthcare workers do not wash their hands before and after each contact with patients; however, this unwanted chain of events can be simply and conveniently broken through effective use of hand hygiene (Reyaz, Gupta, and Sisodia 2020). Therefore, exclusive emphasis has been placed on hand hygiene, where the Centers for Disease Control and Prevention of the US Department of Health and Human Services recommends disinfection with products based on alcohol or washing with soap and water if hands are visually dirty (Iwanowicz-Palus et al. 2019). In accordance with the aforementioned, in this study a review

of the literature of the last 10 years was carried out to show fungal agents present on HCW-H. The information presented not only summarizes the current understanding of the presence of fungi on HCW-H, but also provides information on the methods that were used for the identification of fungi and the relationship on the effectiveness of hand washing with the appearance of fungi on HCW-H.

Materials and Methods

Protocol and registration

A PROSPERO-registered systematic review (CRD42021224411) was conducted following the PRISMA statements (Moher et al. 2009) to report the study protocol and objectives of the current knowledge on the fungal agents present HCW-H.

Eligibility criteria

Research articles included in the study were those that: 1) evidenced the presence of at least one fungal agent on HCW-H, 2) mentioned methods of fungi identification, 3) identified fungi with clinical relevance and 4) emphasized hand washing as a safe alternative to prevent the spread of fungal agents. Review articles, metaanalysis, scientific event reports, books, book chapters, and guides were excluded from the analysis.

Search and selection

Proquest, ScienceDirect, Scielo, Pubmed and Springer databases were searched from 2010 to 2020 for studies involving the presence of fungal agents on HCW-H. Search was carried out only in English using keywords such as Hand and Healthcare workers as base; additionally, search was refined by separately adding words such as Fungi, Yeast or *Candida* spp. to base words, respectively. Search was accomplished using the Boolean operator AND. Given that several information included the presence of bacterial agents on HCW-H, the search was refined by excluding the word Bacteria through the Boolean operator NOT. This refinement was used in databases such as Proquest, Pubmed and Springer, where the number of articles exceeded 1000 records.

Data selection and risk of bias in individual studies

Two authors performed the search independently applying the established keywords and strategies. All titles and abstracts that were identified using the aforementioned search engines were included for analysis. Data were recorded using a standardized bibliographic matrix considering variables such as population, sample size, isolated fungi, quantitation method, clinic relevance and handwashing importance. Data were obtained by means of tabulation in order to organize and identify the relevant information about fungal agents present on HCW-H. Two authors independently assessed the risk of bias of included studies, based on the following elements: random sequence generation, blinding, incomplete data and results, and other sources of bias. Finally, two authors reviewed the quality of included data, type of data included, duplication of studies, blinding, and other sources of bias.

Statistical analysis

The Mantel-Haenszel statistical method was implemented to analyze the dichotomous data, considering the risk ratios (RR) with 95% of confidence interval (CI). Heterogeneity among studies was estimated using I^2 statistic and substantial heterogeneity was represented by an I^2>50%. A fixed effects model was used if heterogeneity test did not reveal statistical significance (I^2 < 50%, $P > 0.1$). Otherwise, we adopted the random effects model. The statistical program Revman 5.4.1 (Cochrane, London, UK) was used for the analyzes and a value of $p < 0.05$ was used as a threshold to determine the statistical significance.

Results

Study selection

The initial search yielded 2481 documents, where 1145 were found in Proquest, 558 in Pubmed, 484 in ScienceDirect, 281 in Springer and 10 in Scielo. After reading titles and abstracts, 2356 documents that did not mention the presence of fungal agents on HCW-H were excluded. Later, 99 manuscripts were excluded, since several mentioned the appearance of fungal agents, but not on HCW-H, and other documents were emphasized on bacteria. Then, 7 studies were excluded due to duplication, leaving 19 eligible research articles. Additionally, 3 articles were obtained from other sources, which were included in this study. In summary, 22 scientific articles were found on the presence of fungal agents on HCW-H. These 22 articles were read completely in order to extract all the necessary information, leaving only 6 articles that met all eligibility criteria (**Figure 1**).

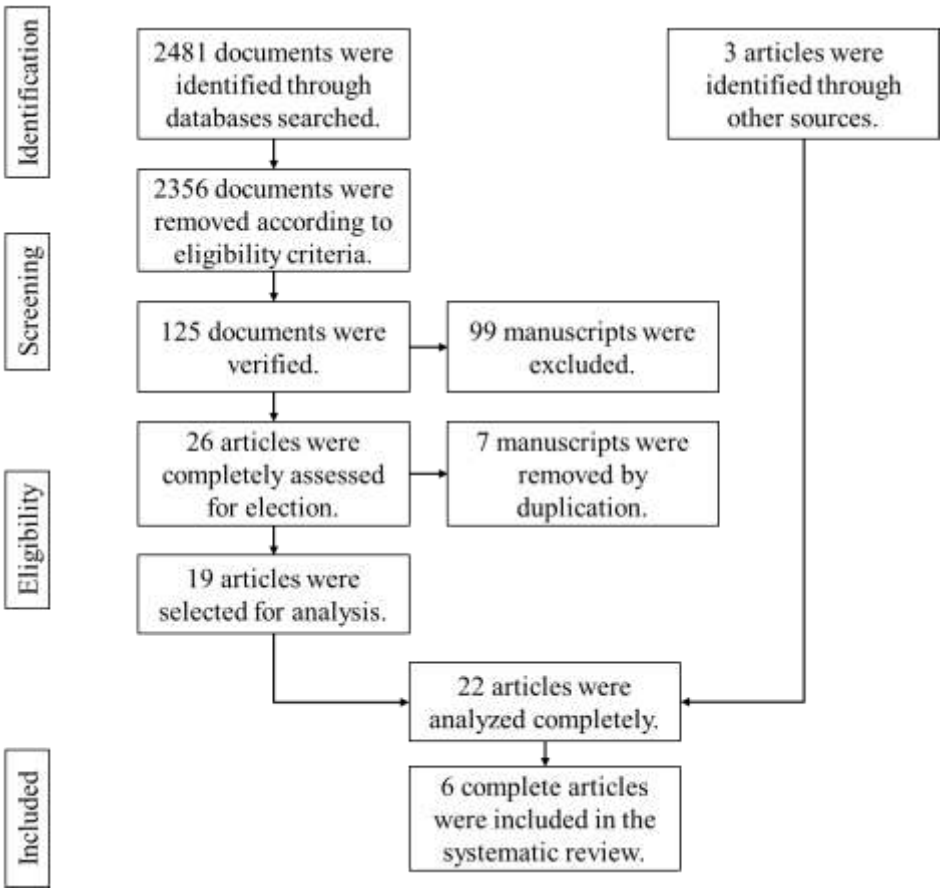

Figure 1. Flow chart for studies selection.

Study characteristics

Fungal strains isolated from HCW-H are shown in table 1. In the study developed by Sun et al., isolated fungi distribution indicated that *Saccharomyces cerevisae* had the highest frequency of occurrence. The percentage of isolated *S. cerevisae* was 61.8% (n = 21), while other isolated fungi were *Penicillium chrysogenum* and *Aspergillus niger* (n = 13, 38.2%), being *P. chrysogenum* the one that registered the lowest frequency of appearance (n = 6, 17.6%) (Sun et al. 2016). On the other hand, De Paula Menezes et al., identified the production of *Candida spp.* biofilms isolated from HCW-H from a neonatal ICU. Results elucidated the presence of *C. parapsilosis sensu stricto, C. metapsilosis, C. orthopsilosis, C. albicans, C. famata, C.*

lusitaniae, C. krusei, C. kefyr, C. tropicalis, C. glabrata and *C. guilliermondii* (De Paula Menezes et al. 2019). In other study, 40 healthcare workers were monitored and 126 samples (80 hands and 46 rings) were obtained before and after medical care. Results showed that 27.7% of samples were colonized by fungi. The species found were *Candida* spp., (16.6%), *Rhodotorula* spp., (3.9%), *Aspergillus niger* (3.1%) and *Aspergillus flavus* (3.9%). Most of the *Candida* spp. species included: *C. albicans* (65%), *C. tropicalis* (18%), *C. glabrata* (12%), and *C. krusei* (5%) (Khodavaisy et al. 2011). In the work performed by Brühwasser et al., samples were collected from 154 HCW-H (79 women and 75 men). Results evidenced the isolation of eleven *Candida* spp. species (7.1%) from HCW-H as follows; *C. parapsilosis* (n = 4), *C. tropicalis* (n = 3), *C. albicans* (n = 2), *C. glabrata* (n = 1) and *C. guillermondii* (n = 1) (Eksi et al. 2010). In a surveillance study, the presence of fungi in ICU and intermediate ICU was analyzed. Ten health workers from ICU and 10 from intermediate ICU were randomly selected, and sampling was carried out during working hours without prior notification. Compliance with hand hygiene was assessed by applying the recommendations of WHO compliance program. Results elucidated that nine health workers (5 nurses and 4 doctors) had yeast on their hands, including *C. albicans* (n = 1), *C. glabrata* (n = 1), *C. guilliermondii* (n = 1), *C. orthopsilosis* (n = 3) and *Malassezia furfur* (n = 3) (Brühwasser et al. 2016). Finally, in the study developed by Naeem et al., samples of the dominant hand of 40 dentists were collected in the middle of the workday, shortly after removing gloves and performing professional hand cleaning. Potentially pathogenic fungi found were *C. albicans*, *Aspergillus niger* and *Aspergillus flavus* (Naeem et al. 2015).

Table 1. Fungi isolated from HCW-H.

Population	Sample from HCW-H	Fungi isolated	Reference
Traditional Chinese Medicine Doctors	265	Fungi were found as follows: *S. cerevisae* 61.8% (n = 21), P*enicillium chrysogenum* and *Aspergillus niger* (n = 13, 38.2%) and *P. chrysogenum* (n = 6, 17.6%). Yeasts were found in 34 (12.8%) of 265 samples.	(Sun et al. 2016)
Healthcare personnel	134	Fungi were found as follows: 19 *C. parapsilosis*, 3 *C. metapsilosis*, 1 *C. orthopsilosis*, 7 *C. albicans*, 6 *C. famata*, 5 *C. lusitaniae*, 3 *C. krusei*, 2 *C. kefyr*, 2 *C. tropicalis*, 1 *C. glabrata*, and 1 *C. guilliermondii*. 49 (98%) isolates expressed at least one of the 3 factors studied and 17 (34%) expressed them all simultaneously.	(De Paula Menezes et al. 2019)
Nurses, nursing assistants, physician, and orderlies	40 plus 29 and 17 rings before and after clinical procedures, respectively	Fungi were found in HCW-H and rings (n = 126) as follows: 16.6% *Candida* spp., 3.9% *Rhodotorula* spp., 3.1% *Aspergillus niger*, and 3.9% *Aspergillus flavus*. The most widely isolated *Candida* ssp. species included: *C. albicans* (65%), *C. tropicalis* (18%), *C. glabrata* (12%), and *C. krusei* (5%).	(Khodavaisy et al. 2011).

Healthcare personnel	154	Fungi were found in HCW-H (n = 47; 30.5%) as follows; 11 *Candida* spp., 4 *C. parapsilosis*, 3 *C. tropicalis*, 2 *C. albicans*, 1 *C. glabrata* and 1 *C. guillermondii*.	(Eksi et al. 2010)
Healthcare personnel	80	Fungi were found in 9 HCW-H as follows: 1 *C. albicans*, 1 *C. glabrata*, 1 *C. guilliermondii*, 3 *C. orthopsilosis*, and 3 *Malassezia furfur*.	(Brühwasser et al. 2016)
Healthcare personnel (dentists)	20 without rings and 20 with rings	Fungi were found in 79% of samples from hands with rings, compared to 21% of samples from hands without rings, as follows: *Candida* spp. (40%), *Aspergillus niger* (7.4%) and *Aspergillus flavus* (5%).	(Naeem et al. 2015)

Considering the presence of fungi on HCW-H, it is important to highlight both the clinical importance and the relevance of handwashing to prevent the spread of agents (Table 2). Fungi such as *S. cerevisae*, *P. chrysogenum*, *A. niger*. and *P. chrysogenum* have clinical relevance in the appearance of keratitis and endophthalmitis (Sun et al. 2016). In other study, the presence of *C. albicans* was confirmed in a very low-weight premature newborn, who died at birth after acquiring the infection (De Paula Menezes et al. 2019). One of the vectors for the host of fungi are rings, since they increase the risk of *Candida* spp., which may cause septicemia, urinary tract infections or SSI (Khodavaisy et al. 2011); in fact, fungi such as *C. albicans* have been detected in dentists' rings after performing handwashing (Naeem et al. 2015). Likewise, *C. parapsilosis* is considered the most frequent fungus on HCW-H and the one that spreads most frequently (Brühwasser et al. 2016; Eksi et al. 2010).

Table 2. Methods used for fungi isolation from HCW-H. Fungi identification with clinical relevance and the importance of handwashing.

Identification method	Clinical relevance	Importance of handwashing	Reference
1) Counting UFC by dilution method and sowing by casting on nutrient agar at room temperature for 48 hrs. 2) Sowing direct swab on nutrient agar and PDA. Identification by microscopic and macroscopic characteristics according to taxonomic keys. 3) Sensitivity tests by disk diffusion technique.	• *S. cerevisae, P. chrysogenum, A. niger* and *P. chrysogenum in keratitis and endophthalmitis.* • *A. niger* in skin infections. • *S. cerevisae* isolated from blood cultures, bronchopneumonia, and catheter contamination. • *P. chrysogenum* in opportunistic infections of immunosuppressed patients: pneumonia, localized granulomas, "fungal balls", systematic infection, allergen and asthma inducer.	*S. cerevisae* infections are associated with medical care due to improper handwashing by physicians. Existing fungi can cause mycosis in different people with variable habits; especially in immunosuppressed patients.	(Sun et al. 2016)
1) Sowing on Sabouraud dextrose agar plus chloramphenicol and chromium gene agar at 30 °C for 72 hrs. 2) Identification of yeasts using germ tubes. *C. albicans* was confirmed by PCR. 3) Detection of hemolytic and DNase activities and biofilm formation assays to witness virulence factors. 4) Antibiotic resistance test.	• *C. albicans* was involved in an infection that caused death of a neonate in the same study. • *C. famata* is present on HCW-H. It is an emerging species in a hospital environment that significantly expressed hemolytic, DNase and biofilm activity. Its management in newborn management units is important. • The hemolysins present in some strains allow greater survival in the host.	Inadequate hand hygiene of health personnel is one of the main forms of horizontal transmission of microorganisms responsible for invasive infections in critically ill patients, such as newborns. The results show the need for greater rigor in the practice of hand hygiene to control infections.	(De Paula Menezes et al. 2019)
1) Swabs were seeded on blood agar, methylene blue eosin and sabouraud dextrose agar at 28 °C for 48 hrs. Swabs	• The lack of use of gloves and use of rings were associated as a risk factor that increases the presence of microbial. The largest fungus	The application of proper handwashing techniques is recommended. Removal of rings,	(Khodavaisy et al. 2011)

were seeded on a chromoagar for *Candida* spp. 2) Fungi were identified using standard microbiological procedures.	isolated was *Candida* spp., which may cause septicemia, urinary tract infections, or SSI.	watches and bracelets before handwashing minimizes the transmission of disease.	
1) Sample (0.1 mL) was seeded in blood agar and sabouraud agar with chloramphenicol and gentamicin at 37 °C for 7 days. 2) Antifungal susceptibility was performed with the ATB Fungus 2 kit.	• The *C. parapsilosis* strain is an important pathogen involved in the transmission of diseases through HCW-H.	The flora on HCW-H is significant in the development of nosocomial infections.	(Eksi et al. 2010)
1) Sample was seeded on agar with malt extract, chloramphenicol and blood agar at 28 °C for 5 days. 2) Identification was done using a Vitek and by mass spectrometry. 3) Genetic relationship between *Candida* isolates was determined by using random amplified polymorphic DNA.	• Low incidence of yeast detected on HCW-H in ICU contrasts with the incidence reported in previous studies, in which glove juice methods were used for sampling. *C. parapsilosis* is considered the most frequent species found on hands; therefore, this fungal is transmitted easier.	Higher contamination was observed in doctors than in nurses. This indicates that there is greater adherence to handwashing protocols by nurses.	(Brühwasser et al. 2016)
1) Sample was sown on sabouraud dextrose agar at 28 °C for 48 hrs. 2) Identification was carried out by standard methods.	• The use of rings is related to an increase in fungal contamination, including *C. albicans* as a potential pathogen.	The main focus should be towards improving hand hygiene in order to prevent HAIs globally.	(Naeem et al. 2015)

Results of the metaanalysis

Twelve studies (Brühwasser et al. 2016; Delfino et al. 2014; Eksi et al. 2010; Khodavaisy et al. 2011; Messano 2013; Monistrol et al. 2013; Naeem et al. 2015; De Paula Menezes et al. 2019; Sakita et al. 2017; Storti et al. 2012; Sun et al. 2016; Yildirim et al. 2014) evidenced a total of 1284 healthcare workers that were included within the analysis, where a total of 340 of them reported fungal agents on their hands, while 944 healthcare workers did not evidenced fungi on their hands (**Figure 2**). Overall, presence of fungi on HCW-H was lower in population

studied RR = 0.32 [0.17, 0.60]; however, fungal agents were higher in the studies performed by (Delfino et al. 2014) and (Sakita et al. 2017) with RR = 1.48 [1.15, 1.91] and RR = 1.71 [1.30, 2.26], respectively. Given that there was moderate heterogeneity between studies (I^2 = 97%, *P < 0.0001*), the random effects model was used.

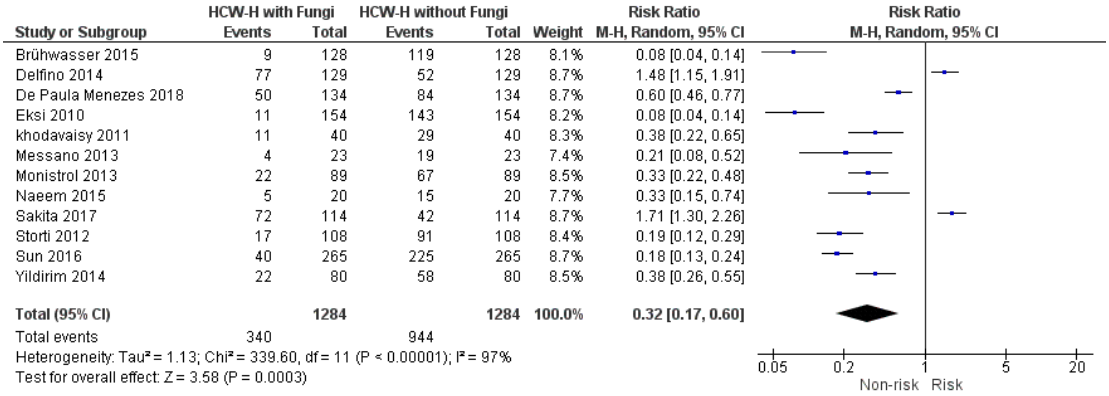

Figure 2. Presence of fungi on HCW-H.

Three studies (Khodavaisy et al. 2011; Messano 2013; Naeem et al. 2015) evidenced a total of 137 healthcare workers included within the studies, where a total of 43 of them who wear rings evidenced fungal agents, while 20 healthcare workers without rings reported fungal agents on their hands (**Figure 3**). Regarding the use of rings by the healthcare personnel during healthcare service, it was elucidated that this accessory represents a risk for healthcare workers who used it compared to those who do not use it RR = 3.33 [2.16, 5.13]. Given that heterogeneity was limited (I^2 = 15%, P = 0.31), a fixed effects model was used.

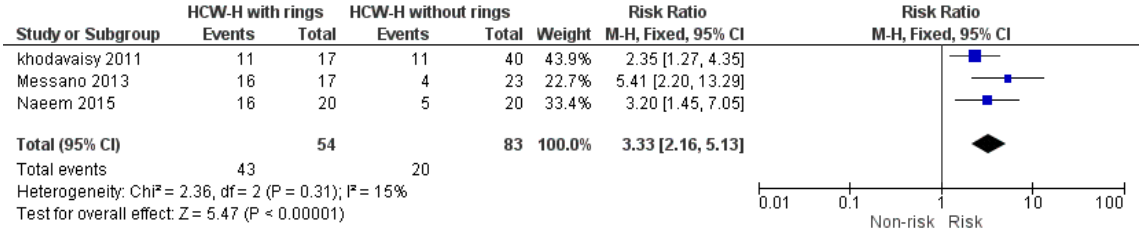

Figure 3. Rings as a vector to host fungi on HCW-H.

A statistical analysis was performed in order to elucidate if fungal agents are presented either in physicians or nurses (**Figure 4**). Results evidenced that three studies evidenced fungal agents on hands of physician and nurses (Brühwasser et al. 2016; Eksi et al. 2010; Storti et al. 2012). Regarding physicians, it was elucidated that 8 presented fungal agents, while 50 of the were free of fungi. Concerning nurses, it was demonstrated that 13 of them presented fungal agents, while 166 of them did not report fungi on their hands. Overall, there is low incidence of fungi on physician RR = 0.16 [0.08, 0.31] and nurses RR = 0.08 [0.05, 0.13]. Given that heterogeneity was limited (I^2 = 12%, P = 0.34), a fixed effects model was used.

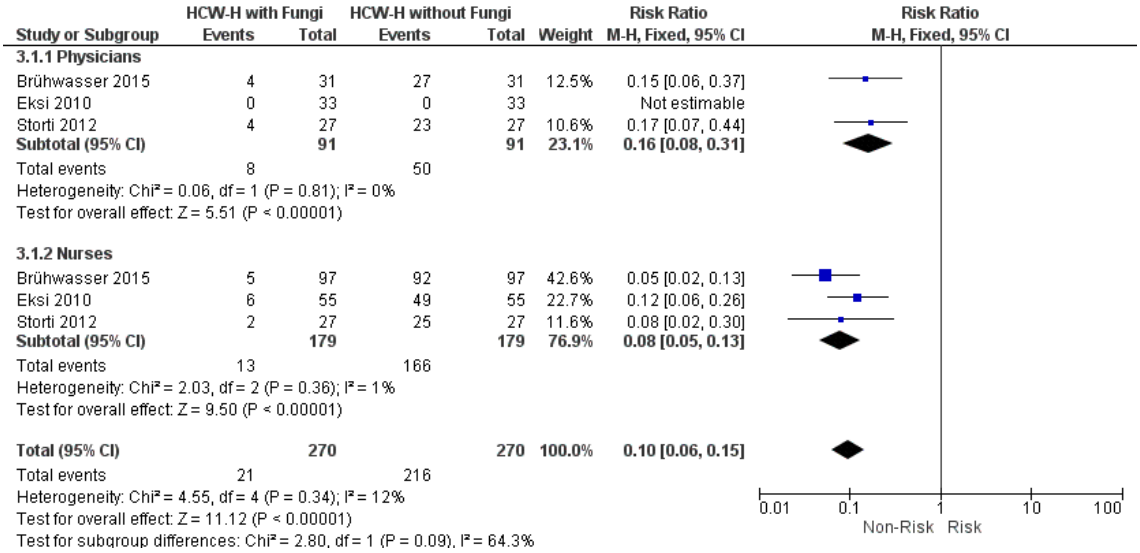

Figure 4. Presence of fungal agents on hands of physicians and nurses.

Discussion

The increase in HAIs in hospitals, especially infections caused by fungal agents, has generated an alert in health systems due to the impact that they generate worldwide on patients health who acquire an infection during their stay in a medical center (Haque et al. 2018; Schmier et al. 2016). This has led to the generation of strategies for preventing and mitigating microorganisms' appearance, such as proper use of antibiotics; however, it is relevant to highlight that clinical resistance to antifungal agents continues to be a challenge for health systems (Al-Khikani 2020). For instance, predominant nosocomial pathogenic fungi such as *Candida* spp., *Aspergillus* spp., *Mucorales*, and *Fusarium* spp., are difficult to diagnose and they cause high morbidity and mortality despite antifungal therapy (Berman and Krysan 2020; Perlroth, Choi, and Spellberg 2007). Another prevention alternative is hand hygiene, which at present has taken on great relevance due to current pandemic caused by the SARS-Cov-2 virus (World Health Organization 2020). since it has been shown that handwashing significantly reduces the spread of HAIs (Sickbert-Bennett et al. 2016). According to Bloomfield et al., hand hygiene is a key component, as it can produce significant benefits in terms of reducing the incidence of infections, especially gastrointestinal infections, but also those of respiratory tract and skin (Bloomfield et al. 2007). Bearing this in mind, it is necessary to know the relationship between the appearance of fungal agents on HCW-H and their relationship with handwashing. Although there are several studies that show fungi isolated from HCW-H (Brühwasser et al. 2016; Eksi et al. 2010; Khodavaisy et al. 2011; Naeem et al. 2015; De Paula Menezes et al. 2019; Sun et al. 2016), there is no evidence in literature that consolidates the clinical relevance that fungi may have and the importance of handwashing to prevent their spread. In this context, this systematic review aims to summarize different contributions of the last 10 years on the presence of fungal agents on HCW-H who practice handwashing.

Fungi that occur most frequently on HCW-H are *S. cerevisae, P. chrysogenum, Aspergillus niger, Aspergillus flavus, Rhodotorula* spp., and *Malassezia furfur*. Additionally, incident episodes of candidemia were evidenced, where *C. parapsilosis sensu stricto, C. metapsilosis, C. orthopsilosis, C. albicans, C. famata, C. lusitaniae, C. krusei, C. kefyr, C. tropicalis, C. glabrata* and *C. guilliermondii* were the most frequent. According to Storti et al., *C. albicans* is the most isolated fungus from HCW-H; in fact, they affirm that most cases of candidemia can not only be caused by a pre-existing colonization in patients, but can also be acquired by manipulation and direct contact with hands of healthcare professionals (Storti et al. 2012). Other types of *Candida* spp. such as *C. parapsilosis (sensu stricto), C. glabrata, C.*

tropicalis and *C. krusei* have been isolated from HCW-H, where *C. glabrata* has presented the highest resistance rates according to antifungal susceptibility tests (Sakita et al. 2017). In the case of *C. Auris*, which has been isolated from hands of ICU workers, it has been described that one of the strategies for its eradication is an adequate training and teaching of handwashing protocols (Biswal et al. 2017). Although handwashing protocols are important for fungi eradication, it has been reported that *Candida* spp. remain on hands after using antimicrobial disinfectants; for example, the rate of candidaemia after applying antiseptics is 10.5% for alcohol-based disinfectants, 4% for chlorhexidine gluconate, 7.5% for povidone iodine, and 50% for commercial soap (Yildirim et al. 2014). However, it is vitally important to intensify cleaning routines and place greater emphasis on the adequacy of the length, frequency and specific care when cleaning surfaces, as this would reduce the spread of pathogens (Pastor et al. 2012). Fungi are also reflected by the use of accessories such as rings (Khodavaisy et al. 2011; Naeem et al. 2015), where the presence of fungi such as *C. albicans, Aspergillus niger* and *Aspergillus flavus* has been evidenced (Messano 2013). For this reason, it is important to generate campaigns to improve compliance with hand hygiene during medical care, since it has been described that these events reduce risk factors caused by the use of long nails or rings (Monistrol et al. 2013). It is relevant to mention that hygiene protocols must be extrapolated to all health personnel, since it has been evidenced the presence of yeast in doctors, nurses, orderlies and postgraduate medical students, whose hands have been colonized by fungi; in fact, health personnel working in general, cardiovascular or neonatal ICU tend to be positive for different types of fungi such as *C. parapsilosis, C. albicans, C. glabrata, C. tropicalis, C. lambica, C. lusitaniae* and *C. krusei* (Delfino et al. 2014).

Accordingly, candidemia is the predominant fungal agent on HCW-H, with *C. parapsilosis* and *C. albicans* being the most frequent yeasts (Brühwasser et al. 2016; Eksi et al. 2010; Naeem et al. 2015; De Paula Menezes et al. 2019). The repercussions generated by the appearance of *Candida* spp. on health can be reflected in septicemia, urinary tract infections or SSI (Khodavaisy et al. 2011). According to a survey by the Swiss Fungal Infections Network, one third of all episodes of bloodstream infections caused by *Candida* spp. occur in patients admitted to ICU (Marchetti et al. 2004). For example, *C. parapsilosis* has been described as an important pathogen, since it implies the possibility of nosocomial transmission of fungemia through HCW-H (Eksi et al. 2010; Levin et al. 1998); exactly, through direct interaction between nurses and patients (Lupetti et al. 2002). Another fungal agent found on HCW-H was *C. Famata* (De Paula Menezes et al. 2019), considered a rare yeast in invasive infections and in the microbiota of healthy individuals (Beyda et al. 2013). Nevertheless, it is relevant to control the spread of this yeast since it has been shown to affect newborns who are in the neonatal ICU (Shilpee, Suresh, and Roopa 2015). Fungi such as *P. chrysogenum* have been linked as agents of keratitis and endophthalmitis, while *A. niger* causes skin infections (Coutinho, Cavalcanti, and Cordeiro Neto 2007). Moreover, the pathogen *P. chrysogenum* has been observed in people with severely suppressed immune systems, such as those with human immunodeficiency virus (HIV), causing infections such as pneumonia, granulomas, fungal balls and systematic infections (Sun et al. 2016) or acting as an allergen and asthma inducer (Barcus, Burdette, and Herchline 2005). In the case of the microbe *S. cerevisiae*, it has been found in blood cultures of immunocompetent subjects (Enache-Angoulvant and Hennequin 2005); in fact, *S. cerevisiae* has been recognized as a transient colonizing fungus of gastrointestinal mucosa, female genital tract, and respiratory tract (Enache-Angoulvant and Hennequin 2005; Silva et al. 2011). Considering the mentioned above, there are several challenges associated with preventing outbreaks caused by IFIs, including rapid diagnostic methods, adherence to infection control practices, and awareness of healthcare providers (Benedict et al. 2017).

There are limitations in the studies that considered the presence of microorganisms and their role in HAIs appearance. Variables that must be considered are several, which leads to a discrepancy between the published studies. For this reason, there is a necessity to go deeper into this topic; for instance, Messano et al., suggested conducting studies with a larger sample quantity (Messano 2013), while Brühwasser et al., indicated that low incidence of yeasts detected could be caused by sampling method, which could be the direct impression of fingertips on agar instead of the glove juice method (Brühwasser et al. 2016), implemented by (Strausbaugh et al. 1994) and (Creamer et al. 2010), who reported a higher incidence, since samples were not only taken from fingertips, but from entire extension of the hand. Other investigations should include whether microorganisms found on HCW-H come from workers themselves, or whether they are mobilized through contamination of surfaces, leading to testing of which of both strategies (hand hygiene or surface disinfection) have greatest impact (Pastor et al. 2012). On the other hand, it has been emphasized the importance of studying not only the appearance of yeasts on HCW-H, but also knowing the virulence factors expressed by these microorganisms such as drug resistance, adherence, formation of biofilms and presence of a germ tube (Sakita et al. 2017). In this sense, De Paula Menezes et al., agree that virulence factors are especially important when it comes to *Candida* spp. (De Paula Menezes et al. 2019). Finally, use of rings, time spent with gloves and hand hygiene before and after having contact with patients are factors that generate bias in studies, since these factors are related to the presence of microorganisms and therefore in the increase of HAIs (Khodavaisy et al. 2011; Naeem et al. 2015).

Handwashing is one of the main strategies to prevent fungi transmission and; therefore, appearance of HAIs. It is important to periodically monitor health personnel in practice, adherence and knowledge about hand washing. Likewise, it is relevant to focus research on determining the fungal agents isolated not only from HCW-H, but also from different hospital areas. This could be essential to determine the resistance and susceptibility profiles and other virulence factors expressed by fungi. This information could be crucial to reduce fungal infections associated with health care.

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