Indoor hospital air and the impact of ventilation on bioaerosols: a systematic review

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Summary

Hospital-acquired infections (HAI) continue to persist in hospitals, despite the use of increasingly strict infection control precautions. Opportunistic airborne transmission of potentially pathogenic bioaerosols may be one possible reason for this persistence. Therefore, we aimed to systematically review the concentrations and compositions of indoor bioaerosols in different areas within hospitals and the effects of different ventilation systems. Electronic databases (Medline and Web of Science) were searched to identify articles of interest. The search was restricted to articles published from 2000 to 2017 in English. Aggregate data was used to examine the differences in mean colony forming units per cubic metre (CFU/m^3) between different hospital areas and ventilation types. A total of 36 journal articles met the eligibility criteria. The mean total bioaerosol concentrations in the different areas of the hospitals were highest in the inpatient facilities (77 CFU/m^3, 95% confidence interval (CI), 55-108) compared with the restricted (4 CFU/m^3, 95% CI, 10-15) and public areas (14 CFU/m^3, 95% CI, 10-19). Hospital areas with natural ventilation had the highest total bioaerosol concentrations (201 CFU/m^3, 95% CI, 135-300) compared with areas using conventional mechanical ventilation systems (20 CFU/m^3, 95% CI, 16-24). Hospital areas using sophisticated mechanical ventilation systems (such as increased air changes per hour, directional flow and filtration systems) had the lowest total bioaerosol concentrations (9 CFU/m^3, 95% CI, 7-13). Operating sophisticated mechanical ventilation systems in hospitals contributes to improved indoor air quality within hospitals, which assists in reducing the risk of airborne transmission of HAI.

Introduction

Standard infection control precautions are employed to prevent the transmission of infections in hospitals, and include hand hygiene and cleaning as well as targeted transmission-based preventative strategies based on the route of infection spread [1-3]. In hospitals, infection spread often occurs by one or more of three transmission modes: contact, droplet and airborne [2]. Contact transmission occurs by contact with an infectious person (direct) or through contaminated fomites (indirect), but the spread of infection via droplet or airborne transmission is much more difficult to ascertain. Droplet transmission may occur by the release of infectious droplets larger than about five microns whereas airborne transmission may occur by the release of infectious droplet nuclei smaller than about five microns [2], although in practice these definitions are somewhat arbitrary and the processes underpinning their formation are complex. For example, droplets can reduce in size to droplet nuclei when exposed to environmental conditions (i.e., lower humidity) outside of the infected person [4]. Droplet nuclei particles can remain suspended in the air for extended periods [5] and are likely involved in airborne transmission in indoor environments [6-8].

Inadequate indoor air ventilation has been associated with outbreaks of infection in clinical and non-clinical settings [9-11]. Increasing the ventilation rate has been suggested to be an effective management strategy to reduce the risk of infection spread [12, 13]. In hospitals, the potential risk of infection spread is ever present and it has been recommended that indoor air of hospitals be supplied through mechanical ventilation [14]. Areas in the hospital which house patients most susceptible to infections (e.g., operating theatre rooms, transplant facilities, intensive care units) or those with communicable diseases (e.g., infectious or isolation rooms/wards) often have enhanced mechanical ventilation systems in operation. Enhanced features of the mechanical ventilation systems can include increased ventilation rates, pressure differentials, that may be either negative or positive ventilation, and airflow patterns (recirculated air and air exhaust outlets) [14] to remove potential pathogenic bioaerosols from the indoor hospital air; thereby, reducing the risk of infection spread.

Airborne transmission precautions are enforced during hospital admission for a select few infections including tuberculosis [15], measles [16] and varicella infections [17]. However, evidence of other infections being opportunistically spread through the air has emerged such as influenza [18], respiratory syncytial virus (RSV) [19], and *Bordetella pertussis* [20], as well as non-respiratory infections such as norovirus [21], meticillin-resistant *Staphylococcus aureus* (MRSA) [22], and *Clostridium difficile* [23, 24]. Airborne pathogens occurring indoors are often of indoor-generated origin (either from humans or non-human sources) or from the surrounding outdoor air [6].

Furthermore, mechanical ventilation systems often used in hospitals can artificially create or continue to re-suspend bioaerosols (particles containing viable microorganisms), thereby increasing the likelihood of opportunistic airborne transmission [6, 25]; however, unmaintained ventilation systems can harbour microorganisms which can be sheared into the air [6] potentially contributing to the spread of hospital-acquired infections in healthcare facilities [8]. While a recent review reported that bioaerosol composition varied widely in healthcare and dental services [26], the review did not focus on the viability of microorganisms, which is relevant to understanding if they are potentially involved in airborne transmission of hospital-acquired infections.

Bioaerosols are commonly collected using active air sampling techniques. Active air sampling is advantageous compared to passive air sampling techniques but requires specialised equipment and trained staff to operate [27]. Where passive air sampling techniques provide qualitative data alone, the active air sampling provides qualitative and quantitative data. Active air samplers are also useful for enhancing the sensitivity of the detection of bioaerosols where the concentrations are low. Active air samplers work by drawing a known volume of air into the samplers across culture media. Any airborne microorganisms in the sampled air are then deposited onto the culture media and incubated. After appropriate incubation conditions, the colony forming units (CFU) cultured on the media are enumerated and reported using the standard measurement of CFU per cubic metre (CFU/m^3).

The primary aim was to undertake a systematic review to determine the concentration of the microbes (expressed as CFU/m^3) recovered from the indoor air of hospital facilities. Furthermore, we aimed to determine if the ventilation used in hospitals influences these microbial bioaerosol concentrations.

Methods

Our research questions were:

1. What is the microbial concentration of bioaerosols recovered from indoor hospital air using active air sampling techniques?
2. Does the use of mechanical ventilation systems affect the microbial bioaerosol concentrations in indoor hospital air?

Search Strategy

We conducted a literature search of Medline and Web of Science in May 2018 (keywords listed in Supplementary Table A.1 and A.2). The principles of the Preferred Reporting Items for Systematic

Reviews and Meta-Analyses (PRISMA) criteria were adopted. All data used in the review were extracted from published papers.

Selection Criteria

Two authors (R.E.S. & S.C.B.) assessed each journal article for suitability during the first round via screening of titles and abstracts. If eligible, the full-text journal articles were retrieved and reviewed to determine eligibility against detailed inclusion criteria in the second round. Where there was a difference in eligibility assessment, the article was adjudicated by an additional reviewer (L.D.K.).

Inclusion and Exclusion criteria

Studies needed to meet all of the following inclusion criteria: 1) published (in English) between January 2000 and December 2017; 2) air sampling was undertaken indoors in the hospital using inertial impaction methods; 3) air sampling was conducted in a hospital actively providing clinical care; 4) culture of microorganisms used non-selective media (bacterial and/or fungal) consequently reducing reporting bias and; 5) quantitatively reported the results using the standard bioaerosol measurement units (CFU/m^3).

Journal articles were excluded if: 1) standard bioaerosol measurements (CFU/m^3) were not reported or provided data relating to specific microorganisms only (e.g. results limited to Staphylococcus bioaerosols) or; 2) were non-original articles (e.g. reviews) or abstracts or; 3) compared different approaches to air sampling or microorganism culturing techniques (including the testing of new air samplers or culturing techniques) or; 4) sampled air by methods other than inertial impaction methods (e.g. settle plates, filtration, suction samplers) or; 5) compared different effects of mechanical ventilation systems.

Data extraction

Pathogens were categorised as bacterial or fungal. Each row in the dataset contained details relating to the CFU/m^3 result, organism type and genus, hospital area where the air was sampled, if ventilation systems were used, and if so, the type of system operated. For some studies, there was a mean CFU/m^3 reported for multiple organisms and ventilation systems; a separate row in the dataset was used for each. Microorganism genus was categorised if these details were available. Bacterial isolates were also classified as Gram-positive or Gram-negative. The hospital location where samples were collected was categorised into inpatient facilities (inpatient hospital rooms), restricted, or public (publicly accessible areas). Restricted rooms were defined as hospital rooms with restricted access and/or requiring wearing of personal protective equipment such as operating

theatres, intensive care units, haematology or oncology wards. The type of ventilation used in each room was defined as mechanical, enhanced mechanical, or natural. Mechanical ventilation was defined as a system which circulates fresh and recycled air through ducts via air handling equipment, while enhanced ventilation was defined as the mechanical ventilation system operating with extra features (e.g., directional or laminar flow; increased air changes per hour; disinfection treatment of air; HEPA-filtration system). Natural ventilation was defined as ventilation based solely on airflow provided by open doors and windows and an absence of mechanical ventilation.

Statistical analysis

The data were analysed using SPSS version 23.0 (IBM Corp). The dependent variable was the mean CFU/m^3. A traditional meta-analysis could not be completed due to the frequent absence of information around sample size (number of air samples taken at each location and/or the number of locations included in the mean or median calculations) and variability. Instead, the role of location within a hospital and ventilation type on the mean CFU/m^3 was assessed on the $\log_{10}$ transformed data by one-way ANOVA and protected LSD testing for pairwise differences between groups. No adjustments were made to account for sample size, the journal articles or multiple comparisons. The back-transformed geometric mean in CFU/m^3 and 95% confidence intervals are reported. A p value <0.05 was considered significant.

Based on sensitivity analysis using the Student t-test the following combined categories were made for the type of ventilation where mixed ventilation types were described in studies: “natural and mechanical” was coded as “mechanical” ventilation and “mechanical and enhanced mechanical” was coded as “enhanced mechanical” ventilation. If data relating to the microorganisms genus was available and considered clinically relevant but frequencies were less than 10, it was considered missing data.

Results

Article selection

The study selection process is shown in Figure 1. A total of 1256 articles were identified, and after eligibility screening, 92 full-text articles were reviewed. The reviewers disagreed on eligibility of nine articles. Mean or median CFU/m^3 data was extracted from 36 full-text articles eligible for inclusion into the study as well as any data on location of air sampling, genus information and ventilation data if available for the analysis. The characteristics of the 36 articles are reported in Table I.

There were 666 valid CFU/m^3 values available for analysis. Mean CFU/m^3 values were given for 607 data points (32 studies), and of these, only 269 (16 studies) reported standard deviation values. Median values were reported for 59 data points (6 studies). Two studies reported means values for some data points and median values for other data points. Sensitivity analysis using data with both mean and median values recorded (24 data points, 5 studies) showed agreement between the median and mean values in these studies (intra-class correlation coefficient >0.90), giving a small bias of 2.5%. Therefore, the median value was used in place of the mean for the 59 data points without mean CFU values. Only 12 studies (total of 115 data points) reported the number of air samples taken at each location and/or the number of locations included in the mean or median CFU/m^3 (total of 115 data points).

Air sampling conditions

Information about air sampling times was reported in 18/36 (50%) studies and of these, 11/18 (61%) undertook sampling during business hours (peak periods of hospital activity) and 2/18 (11%) reported the specified room was not occupied at the time of measurement. The number of people (including patients) in the rooms at the time of air sampling was provided in 6/36 (17%) studies and of these studies, 5/6 (83%) reported the mean number of people in the room during measurements.

Total bioaerosols within indoor hospital air

The total bioaerosol concentration (mean CFU/m^3) was higher in the inpatient facilities (77, 95% CI 55-108 CFU/m^3) compared with the restricted (4, 95% CI 10-15 CFU/m^3) ($p<0.001$) or public areas (14, 95% CI 10-19 CFU/m^3) of the hospitals ($p<0.001$) (Table II); but was similar between the restricted and public areas of the hospitals ($p=0.57$).

Bacterial bioaerosols

Mean bacterial, Gram-positive and Gram-negative bioaerosol concentrations are shown in Table II. Bacterial bioaerosol concentrations were highest in the inpatient facilities compared with the restricted ($p=0.022$) or public areas of the hospitals ($p=0.003$) but were similar between the restricted and public areas ($p=0.28$). Gram-positive bacterial bioaerosol concentrations were highest in inpatient facilities compared to restricted areas of the hospitals ($p=0.012$); however, there was no significant difference in the Gram-positive bacterial bioaerosol concentrations between inpatient facilities and public areas ($p=0.12$) or between the restricted and public areas ($p=0.22$). Gram-negative bacterial bioaerosol concentrations were higher in public areas compared to restricted areas ($p=0.002$); however, these concentrations were similar between public areas and inpatient facilities ($p=0.38$) and also between inpatient facilities and restricted areas ($p=0.14$).

Staphylococcus spp., *Streptococcus* spp., and *Escherichia* spp. were the dominant bacterial genera identified in the review. Of these bacterial genera, only *Escherichia* spp. had significant differences observed in the different areas of the hospitals. *Escherichia* spp. bioaerosol concentrations were higher in public spaces compared to inpatient facilities (p=0.002) and restricted areas (p=0.004) but were similar between the inpatient facilities and restricted areas (p=0.48). The concentrations of *Streptococcus* spp. and *Staphylococcus* spp. were similar in the inpatient facilities, restricted or public areas (p=0.28 and p=0.38, respectively) (Table II).

Fungal bioaerosols

Mean fungal bioaerosol concentrations are shown in Table II. Fungal bioaerosol concentrations were higher in the inpatient facilities compared to restricted (p<0.001) and public areas (p=0.011); however, the fungal bioaerosol concentrations were similar between the public and restricted areas of the hospitals (p=0.17). *Aspergillus* spp., *Cladosporium* spp., and *Penicillium* spp. were the dominant fungal genera identified in the review. The bioaerosol concentrations of these fungal genera were similar across inpatient facilities, restricted areas and public spaces (p=0.16, p=0.20, p=0.30, respectively) (Table II).

Ventilation comparisons

Areas with natural ventilation (201, 95% CI 135-300 CFU/m^3) had increased total bioaerosol concentrations compared with areas using mechanical (20, 95% CI 16-24 CFU/m^3) (p<0.001) or enhanced (9, 95% CI 7-13 CFU/m^3) mechanical ventilation systems (p<0.001) (Table III). Enhanced mechanical ventilation had similar total bioaerosol concentrations compared to areas with conventional standard mechanical ventilation (p<0.001).

There was no significant difference in the bacterial bioaerosol concentrations in areas with mechanical, enhanced mechanical or natural ventilation (p=0.060) (Table III), but the fungal bioaerosol concentrations were lower in areas using enhanced mechanical ventilation compared to standard mechanical ventilation (p<0.001) or natural ventilation (p<0.001). However, comparisons of areas naturally ventilated or using standard mechanical ventilation systems showed that the fungal bioaerosol concentrations were similar (p=0.12). Mechanically ventilated hospital inpatient facilities had lower total bioaerosol concentrations compared to naturally ventilated inpatient facilities (p<0.001) (Table III). The restricted areas of the hospitals almost exclusively used mechanical ventilation (with two-thirds operating in the enhanced features mode) and restricted areas using enhanced mechanical ventilation had lower total bioaerosol concentrations compared

with standard mechanical ventilation (p=0.014). The public areas of the hospital had similar total bioaerosol concentrations between those using standard mechanical ventilation and those using natural ventilation (p=0.79) (Table III).

Restricted hospital areas

The sub-analyses of restricted areas included a range of clinical settings such as operating rooms, intensive care units, haematology/transplant wards, radiotherapy/chemotherapy wards, and unknown areas which are described as restricted but with limited description provided (called here "unknown") Haematology/transplant hospital areas had significantly lower mean CFU compared to the other restricted areas highlighted above (Table IV). The mean CFU for the restricted hospital area was 18 (95% CI 14 – 22) when Transplant/Haematology wards were excluded.

Discussion

Significant advances in technology and patient management have been made in preventing HAI, yet transmission persists [28, 29] and is associated with increased costs and increased length of stay during hospital admissions [30]. The circulating air in hospitals is one possible route of opportunistic transmission of HAI [31, 32]. Our systematic review demonstrates that the indoor air of hospital inpatient facilities had higher total bioaerosol concentrations compared to other hospital areas (restricted or public areas). The multi-bed room arrangements used in inpatient facilities could promote opportunistic airborne transmission [33]. Furthermore, our analysis found that the use (or lack of) a ventilation system affected the total bioaerosol concentrations of the indoor air, with the lowest total bioaerosols concentrations detected in hospital areas operating with enhanced mechanical ventilation systems.

Bacteria such as *Staphylococcus aureus*, *Enterococcus* spp., and *C. difficile* commonly cause HAI [34] and are problematic due to their increased antibiotic-resistance profiles [35]. Our systematic review demonstrated that the bacterial bioaerosol concentrations were higher in the inpatient facilities, but the composition (whether Gram-positive or Gram-negative) did not vary in the different areas of the hospital. Furthermore, the bacterial bioaerosol concentrations were unaffected by the use of specific ventilation systems. Despite bacteria being a common cause of HAI, the three most common bacterial species that were detected in the hospital air are also normal human commensals [36]. While the Gram-positive genera of *Staphylococcus* spp. and *Streptococcus* spp. had similar bioaerosol concentrations in different areas of the hospital [37], the Gram-negative genus of *Escherichia* spp. had elevated bioaerosol concentrations in the public areas of the hospital. All three bacterial genera detected in the indoor hospital air may originate from bioaerosol dispersal during skin shedding (*Staphylococcus* spp. and *Escherchia* spp.) or being released in respiratory secretions during talking (*Streptococcus* spp.) [37, 38]. Importantly, these genera also include potentially pathogenic HAI species such as *S. aureus* and *E. coli* which can include antibiotic-resistant strains [34].

Outbreaks of fungal infections in HAIs can often affect severely immunocompromised patients with serious adverse outcomes [39] and require care in restricted areas of hospitals to reduce the risk of acquisition of fungal and other infections [2]. Our study demonstrated that fungal bioaerosol concentrations were higher in the inpatient facilities of hospitals compared to the restricted and public areas. The increased fungal bioaerosol concentrations is likely due to the increased bed numbers used in inpatient facilities [40] such as those facilities which accommodate patients in multi-bed rooms. Despite the total fungal bioaerosol concentrations being higher in the inpatient

facilities, the predominant fungal genera identified of *Aspergillus* spp., *Cladosporium* spp., and *Penicillium* spp. were similarly distributed between the different areas of the hospital and may be a result of these potentially pathogenic fungi colonising the hospital built environment [41, 42]. Our study also found that hospital areas using enhanced mechanical ventilation systems had reduced fungal bioaerosol concentrations. The restricted areas included in this study almost universally used mechanical ventilation for air supply, often operating in the enhanced features mode, such as the use of HEPA filtration, directional flow and increased air changes per hour. The operation of the ventilation system with these extra functions likely protects those patients who are particularly vulnerable to acquiring infections such as those in transplant units (for example, bone marrow or renal transplant unit) or operating theatres.

The public and restricted areas of the hospitals were found to have similar total bioaerosol concentrations. This result was surprising considering the very different operating conditions in these hospital areas but may be a result of the general busyness of restricted hospital areas. For example, operating rooms have high numbers of staff and multiple patients, with people movement similar to public areas. In comparison, the haematology/transplant wards have a significantly lower mean bioaerosol concentration compared with the other restricted hospital areas. These areas provide care for immunosuppressed patients and usually restrict traffic of people (e.g. one patient is admitted to a hospital room at one time, limited numbers of visitors and the use of enhanced ventilation systems).

To our knowledge, this systematic review was the first to assess the bioaerosol concentration and composition of indoor hospital air and to report on the associations of bioaerosol concentration in indoor hospital air. However, there are limitations. Firstly, a meta-analysis was not a viable option for this review, mostly due to the articles frequently failing to report the sample size and variability around the reported mean values. However, the quantitative data that was available was aggregated to provide overall mean CFU/m^3 estimates of bioaerosol concentrations in indoor hospital air. No adjustments were made to account for sample size, the articles or multiple comparisons and thus, mean CFU/m^3 estimates may be biased. The emphasis of this work is on the apparent trends and the accuracy of numeric estimates around specific microorganism bioaerosol concentration should be interpreted with caution. Secondly, few journal articles detailed the bacterial and fungal composition in indoor hospital air for comparison. Thirdly, other factors which affect the bioaerosol concentrations in the air such as the number of people, the air sampling times, or cleaning routines were not able to be comprehensively studied here due to the inconsistent reporting. Lastly, some well-known HAI pathogens were excluded from the analysis based on our selection criteria as these

organisms require special culturing conditions which do not support the growth of broader microorganisms (for example, *C. difficile)*; therefore, our analyses has not been able to provide comment about these pathogens.

Our paper summarizes the information about bioaerosol concentrations in indoor air of different hospital areas as well as the ventilation system used. Inpatient facilities were more often contaminated with bioaerosols compared with the restricted and public areas of the hospital. However, the hospital areas using sophisticated mechanical ventilation systems had the lowest bioaerosol concentrations. While understanding the bioaerosol concentrations in indoor hospital air is an important aspect, the data obtained for the bioaerosol composition data were limited. Therefore, a broader analysis of bioaerosol compositions in the indoor hospital air would provide further knowledge about indoor hospital air bioaerosols and especially to understand their potential pathogenicity. Overall, the use of mechanical ventilation systems (especially those with enhanced features) improves the indoor hospital air quality and is an important hospital infection control strategy to prevent HAI transmission.

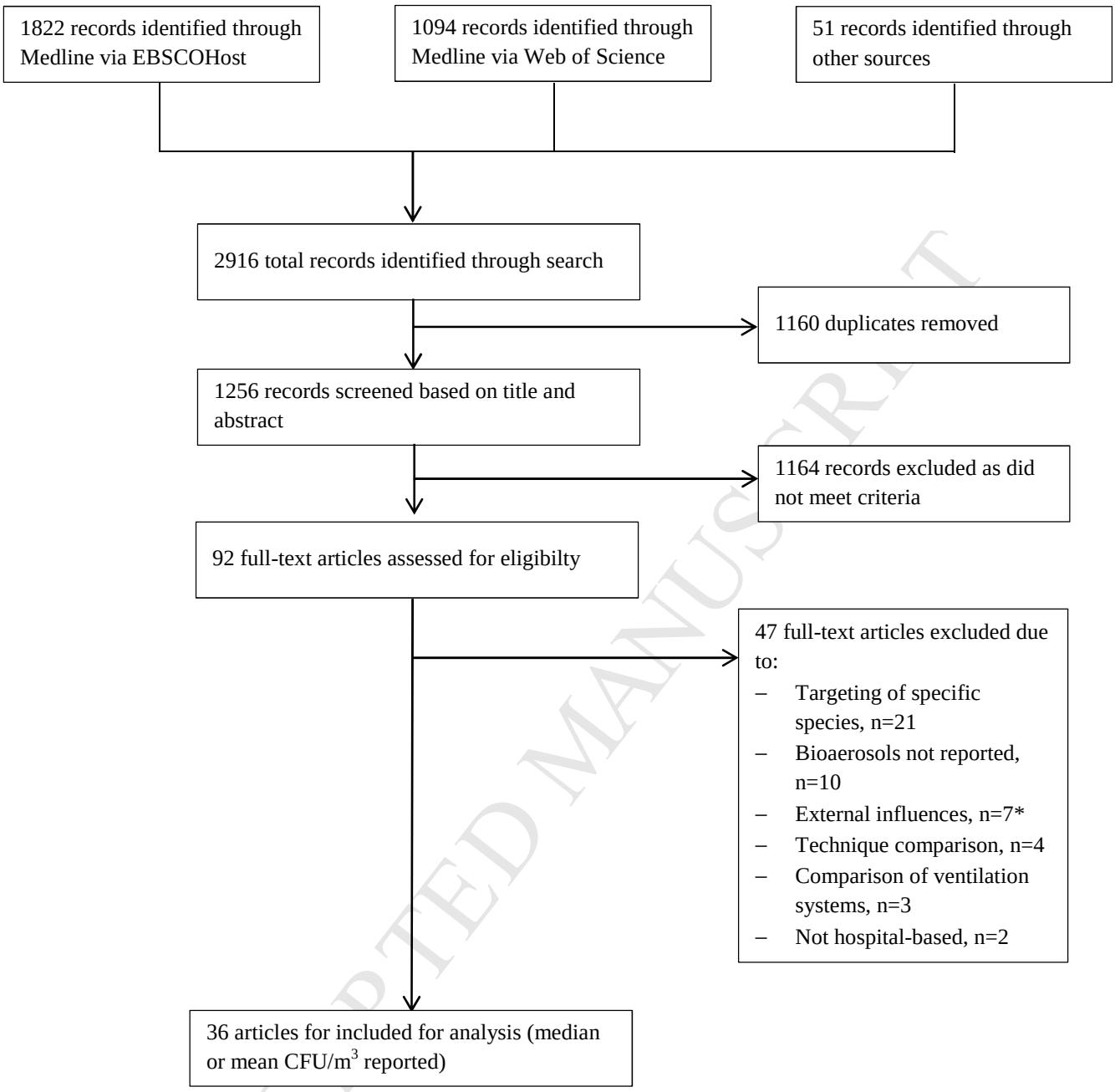

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart for selection of studies

*external influences include renovations (including demolition activity) or any possible aerosol-generating activities in the hospital.

Table I: Characteristics of included studies.

Reference	Microorganism of interest	Hospital locations tested	Ventilation used
[43]	Bacteria only	Hospital passages[~] Outpatient clinics[~] Reception hall[~]	Unknown Unknown Unknown
[44]	Bacteria only	Operating theatre[&]	Enhanced mechanical ventilation
[45]	Bacteria and fungi	Wards[^]	Combination of natural and mechanical ventilation
[46]	Bacteria and fungi	Wards[^]	Natural ventilation
[47]	Bacteria and fungi	Operating theatre[&] Wards[^]	Mechanical ventilation Unknown
[48]	Fungi only	Operating theatre[&]	Unknown
[49]	Fungi only	Restricted, other[%&]	Enhanced mechanical ventilation
[50]	Bacteria only	Operating theatre[&]	Enhanced mechanical ventilation
[51]	Fungi only	Intensive care unit[&]	Unknown
[52]	Fungi only	Radiotherapy ward[&] Intensive therapy[^] Neonatal intensive care unit[&] Chemotherapy ward[&]	Unknown Unknown Unknown Unknown
[53]	Bacteria and fungi	Wards[^] Isolate wards[&] Emergency department[~] Intensive care unit[&] Operating theatre[&]	Combination of ventilation types used Combination of ventilation types used Combination of ventilation types used Combination of ventilation types used Combination of ventilation types used
[54]	Bacteria and fungi	Wards[^] Waiting areas[~] Outpatient department[~] Pharmacy department[~]	Combination of ventilation types used Combination of ventilation types used Combination of ventilation types used Combination of ventilation types used
[55]	Bacteria and fungi	Main lobby[~] Wards[^] Intensive care unit[&]	Mechanical ventilation Mechanical ventilation Mechanical ventilation
[56]	Fungi only	Intensive care unit[&] Neonatology department[&]	Unknown Unknown
[57]	Fungi only	Wards[^]	Unknown
[58]	Bacteria and fungi	Operating theatre[&]	Enhanced mechanical ventilation

[59]	Bacteria only	Operating theatre[&] Wards[^] Intensive care unit[&]	Mechanical ventilation Mechanical ventilation Mechanical ventilation
[60]	Bacteria	Operating theatre[&] Emergency department[~]	Unknown Unknown
[61]	Bacteria and fungi	Operating theatre[&]	Enhanced mechanical ventilation
[62]	Bacteria and fungi	Operating theatre[&]	Enhanced mechanical ventilation
[63]	Bacteria	Operating theatre[&] Ward[^]	Combination of enhanced and conventional mechanical ventilation Unknown
[64]	Fungi only	Wards[^]	Unknown
[65]	Bacteria and fungi	Operating theatre[&] Wards[^]	Enhanced mechanical ventilation Unknown
[66]	Fungi only	Intensive care units[&] Transplant units[&] Wards[^] Corridors[~]	Unknown Unknown Unknown Unknown
[67]	Bacteria and fungi	Operating theatres[&] Corridors[~]	Enhanced mechanical ventilation Mechanical ventilation
[68]	Bacteria and fungi	Restricted, other[%&]	Combination of natural, mechanical and enhanced mechanical ventilation
[69]	Fungi only	Haematology units[&]	Unknown
[70]	Bacteria only	Wards[^] Hall[~] Corridors[~]	Mechanically ventilated Naturally ventilated Naturally ventilated
[71]	Fungi only	Corridors[~]	Unknown
[72]	Fungi only	Intensive care units[&]	Mechanical ventilation
[73]	Fungi only	Haematology units[&]	Combination of enhanced and conventional mechanical ventilation
[74]	Fungi only	Haematology units[&]	Enhanced mechanical ventilation
[75]	Bacteria only	Operating theatres[&]	Enhanced mechanical ventilation
[76]	Fungi only	Wards[^]	Unknown
[77]	Bacteria only	Operating theatres[&]	Enhanced mechanical ventilation
[78]	Bacteria only	Intensive care units[&]	Unknown

[^]inpatient facility; [&]restricted; [~]public; [%]Restricted, other – toilets, corridors, undefined patient care areas.

Table II: Geometric mean colony forming units per cubic metre (CFU/m3) isolated from each hospital area type by pathogen, bacterial gram stain and Genus.

Category			Overall	Hospital area type			p-value
				Inpatient facility	Restricted	Public	
Overall		n (Studies)	528 (36)	129 (14)	267 (28)	132 (10)	<0.001
		mean (95% CI)	21 (17 - 24)	77 (55 - 108)	13 (10 - 15)[a]	14 (10 - 19)[a]	
Pathogen	Bacteria	n (Studies)	244 (17)	48 (8)	115 (13)	81 (7)	0.010
		mean (95% CI)	25 (20 - 31)	47 (26 - 83)	23 (17 - 32)[a]	18 (12 - 26)[a]	
	Fungi	n (Studies)	219 (21)	37 (10)	131 (15)	51 (6)	<0.001
		mean (95% CI)	9 (7 - 11)	23 (12 - 42)	7 (5 - 9)[a]	10 (6 - 16)[a]	
Gram stain category	Gram-positive	n (Studies)	58 (2)	12 (1)	23 (2)	23 (2)	0.040
		mean (95% CI)	11 (8 - 16)	23 (11 - 47)[a]	8 (4 - 13)[b]	12 (7 - 20)[ab]	
	Gram-negative	n (Studies)	45 (4)	7 (2)	16 (3)	22 (3)	0.009
		mean (95% CI)	3 (2 - 4)	3 (0 - 16)[ab]	1 (1 - 2)[a]	5 (3 - 9)[b]	
Bacterial Genus:	*Escherichia*	n (Studies)	18 (3)	2 (1)	3 (2)	13 (3)	0.001
		mean (95% CI)	7 (4 - 11)	1 (1 - 1)[a]	2 (2 - 2)[a]	11 (7 - 16)	
	Streptococcus	n (Studies)	14 (2)	2 (1)	6 (2)	6 (2)	0.28
		mean (95% CI)	3 (2 - 4)	5 (5 - 5)	3 (2 - 4)	3 (1 - 6)	
	Staphylococcus	n (Studies)	12 (2)	2 (1)	5 (2)	5 (2)	0.38
		mean (95% CI)	34 (14 - 82)	110 (12 - 962)	21 (3 - 123)	35 (5 - 211)	
Fungal Genus:	*Aspergillus*	n (Studies)	31 (8)	4 (2)	8 (6)	19 (3)	0.16
		mean (95% CI)	3 (2 - 5)	3 (-1 - 40)	6 (2 - 15)	2 (1 - 4)	
	Cladosporium	n (Studies)	17 (7)	2 (1)	8 (6)	7 (3)	0.20
		mean (95% CI)	19 (12 - 31)	22 (0 - 472)	12 (4 - 32)	30 (16 - 55)	
	Penicillium	n (Studies)	13 (6)	2 (1)	8 (6)	3 (2)	0.30
		mean (95% CI)	13 (8 - 23)	17 (-1 - 1502)	10 (4 - 23)	25 (10 - 59)	

N, number of data points analysed; studies, the number of journal articles reviewed; a, b numbers within points with a letter in common are not significantly different.

Table III: Geometric mean colony forming units per cubic metre (CFU/m^3) isolated from each ventilation type by pathogen and room type.

Category			Overall	Ventilation type			p-value
				Mechanical	Enhanced mechanical	Natural	
Overall		n (Studies)	412 (23)	257 (11)	105 (14)	50 (6)	<0.001
		mean (95% CI)	22 (18 - 26)	20 (16 - 24)	9 (7 - 13)	201 (135 - 300)	
Pathogen	Bacteria	n (Studies)	201 (14)	152 (8)	40 (8)	9 (5)	0.060
		mean (95% CI)	27 (21 - 35)	23 (17 - 31)	46 (31 - 68)	47 (12 - 174)	
	Fungi	n (Studies)	154 (10)	88 (7)	61 (5)	5 (4)	<0.001
		mean (95% CI)	8 (6 - 10)	15 (11 - 20)[a]	3 (2 - 3)	35 (1 - 790)[a]	
Hospital area type	Inpatient facilities	n (Studies)	102 (6)	60 (5)	n/a	42 (4)	<0.001
		mean (95% CI)	69 (47 - 100)	25 (16 - 39)	n/a	284 (200 - 404)	
	Restricted	n (Studies)	210 (19)	103 (6)	105 (14)	2 (1)	0.047
		mean (95% CI)	12 (10 - 15)	16 (12 - 21)[a]	9 (7 - 13)[b]	15 (0 - 365) [ab]	
	Public	n (Studies)	57 (4)	53 (4)	n/a	4 (1)	0.79
		mean (95% CI)	19 (13 - 27)	19 (13 - 28)	n/a	16 (8 - 31)	

Within points, a letter in common is not significantly different. n/a = not applicable.

Table IV: Geometric mean colony forming units per cubic metre (CFU/m^3) isolated from restricted hospital areas sub-analysis.

Restricted area location	**n**	**Geometric mean CFU (95% CI)**
Operating room	93	18 (12 - 26)
Intensive care unit	67	17 (11 - 26)
Transplant/Haematology ward	57	3 (3 - 4)[a]
Radiotherapy/Chemotherapy ward	3	47 (11 - 191)
Unknown but described as restricted	47	18 (12 - 27)

[a]Significantly different from each of the other groups

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