UNIVERSITY OF COPENHAGEN

SYSTEMATIC REVIEW OF THE EFFECTIVENESS OF HEALTHY HOSPITAL INFRASTRUCTURE TO PREVENT HEALTHCARE ACQUIRED INFECTIONS

A dissertation submitted in partial fulfillment of the requirements for the degree of Master of Europubhealth

By

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Supervisor: Dr Elsebeth Tvenstrup Jensen

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ABSTRACT

Background: Healthcare acquired infections (HAIs) are among the major causes of mortality and increased morbidity among hospitalized patients, leading to many Quality-Adjusted Life Year (QALY) losses and economical costs (WHO, 2002). At least 20% of all HAIs are preventable (Harbarth et al. 2003), and hospital infrastructure is identified to be one of the important factors associated with HAIs.

Objective: To systematically review studies on healthy hospital infrastructure for preventing HAIs, and assess the effectiveness of these types of infrastructure in order to guide hospital construction and renovation practice.

Method: Evidence from studies with a study design of Level A and Level B of the NHS ranking of evidence quality were systematically reviewed. OvidSP Medline, PsycINFO, and Embase were searched with defined key words. Articles published in English language and from 1980 onward were screened for inclusion criteria.

Results: Ten studies classified into four hospital infrastructure categories were identified, including seven specific infrastructure types investigated. Among the seven types, the single-bed room was supported by strong evidence to be effective in reducing HAI, and the high ratio of area of ventilation window to the volume of patient room was favored by some evidence to be useful; laminar airflow ventilation had conflicting results; while the other four types were identified by certain evidence to have no benefit for HAI prevention, including ABHR dispensers, computerized voice reminders for handwashing, spacious patient rooms, and copper-silver ionization for water supplying system in hospitals.

Conclusion: Given the identified results, single-bed rooms for acute care units and at least one ventilation window for the patient room in hospitals are strongly advocated. There is currently no strong evidence for recommending the implementation of other hospital infrastructure types for the purpose of reducing HAIs.

Key words: hospital; infrastructure; healthcare acquired infection.

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My idea for this dissertation topic was raised from the investigation I once participated in when I was working at the China CDC, which was an investigation on risk factors for outbreak of infectious diseases in hospitals, schools, and local CDC laboratories. For the hospital part, it was found that the lack of handwashing facilities, turbulent distribution of patient rooms, and inappropriate ventilation might be potential risk factors for HAIs. As there is currently no systematic review about the relationship between hospital infrastructure and HAIs, thus the study was conducted to fill this gap.

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SYSTEMATIC REVIEW OF THE EFFECTIVENESS OF HEALTHY HOSPITAL INFRASTRUCTURE TO PREVENT HEALTHCARE ACQUIRED INFECTIONS

CHAPTER 1: INTRODUCTION

1.1 Background

Healthcare Acquired Infection (HAI) is one of the major problems facing medical services throughout the world. Despite progress and many benefits in hospital modernization and care, infections continue to develop in hospitalized patients and even hospital staff, resulting in numerous losses in Quality-Adjusted Life Year (QALY) and high amount of additional burden and economical costs in healthcare (WHO, 2002). Infections acquired in healthcare settings are among the major causes of death and increased morbidity among hospitalized patients (WHO, 2002). Nosocomial infections occur worldwide and affect both developed and resource-poor countries. At any time, over 1.4 million people worldwide suffer from HAIs (Tikhomirov, 1987). A survey conducted by the WHO in 55 hospitals of 14 countries represented a nosocomial prevalence rate in 4 WHO Regions, namely, Europe (7.7%), Eastern Mediterranean (11.8%), South-East Asia (10%) and Western Pacific (9.0%), and showed that an average of 8.7% of hospital patients had infectious complications acquired in hospital (WHO, 2002).

In Europe, although the prevalence rate is slightly lower than the average level worldwide, these infections contribute to both morbidity and mortality, with many thousands considered to die as a result. A surveillance of HAIs in Europe in 2006 suggested that about 3,000,000 patients acquire a HAI in the EU25 each year, with approximately 50,000 of them die as the consequence of the infection (HELICS, 2006). In Denmark, three prevalence surveys (twice in 2006 and once in 2007) in North Denmark Region found the overall prevalence rate varied between 5.2 and 7.1% (Scheel et al. 2007). While in another study from Petersen et al (2010) including patients admitted to seven departments of internal medicine in Denmark, the overall prevalence of HAI was estimated to be 9.7%. In the UK, data from the third prevalence survey of HAI in acute hospitals estimated

that about 8.6% of patients acquire an infection whilst in hospital (Hospital Infection Society, 2006). And the estimated cost to NHS hospitals of caring for people that acquire a HAI is over £1 billion a year (NAO, 2009). Besides, surveillance of HAIs in Europe performed by the European Centre for Disease Control and Prevention (ECDC) showed a diversity of incidence of surgical site infections and infections acquired in intensive care units (ICUs) among 17 different European countries (ECDC, 2011).

A systematic review in 2003 concluded at least 20% of all HAIs as probably preventable (Harbarth et al. 2003). Similarly, another study by the Hospital in Europe Link for Infection Control through Surveillance (HELICS) also estimated 20 to 30% of HAIs can be prevented by an intensive infection prevention and control programme (HELICS, 2006).

Among all the factors associated with HAIs, hospital infrastructure has a profound effect on health and HAIs in both negative and positive ways. On one side, there are increasing reports of HAIs caused by construction or renovation in facilities (Bartley & Olmsted, 2009). On the other side, there is rapid growth of studies focusing on healthy hospital infrastructure and design for preventing HAI. Today a lot of hospitals are retro-fitted, hospital plans from five Danish regions show a significant renovation programme including green field investments at 5 new sites, significant extension and renovation of several existing hospitals and mergers or closures of several small hospitals (Fulop et al., 2002). While the UK plans to newly build a hundred hospitals and thousands of primary-care clinics and surgery centres (Ulrich, 2006). However, not many of the hospitals applied the existing findings of the infrastructure features in one place. Another reality is that analysis of hospital design is challenging and relatively fewer randomized controlled trials (RCT) were used either because of difficulty to remove confounding variables or the construction condition made it impossible to do a RCT. The various evidences from the studies on hospital infrastructure need careful evaluation. By now there is no systematic review about the healthy hospital infrastructure for HAI prevention, thus there remains a lack of justified and comprehensive evidence over how useful are the variety of studied hospital infrastructure in preventing HAI.

To illustrate, there are still questions like: 1. What are the kinds of infrastructure studied to be effective in prevention of HAIs? 2. How trustable and strong are these evidences? 3. Which percentage in reduction of HAI could be obtained by infrastructure? Or if any 4. What is the cost-effectiveness of these infrastructure interventions?

Thus, this systematic review is based upon this need, and aims to assess all these evidences to facilitate hospital managers and guideline makers to make their best choice for hospital design and construction, in order to reduce the HAI in the long run.

1.2 Definition of terms

1.2.1 Healthcare acquired Infections: Healthcare acquired infections (HAI), means an infection acquired during the course of receiving medical care by a patient who was admitted for a reason other than that infection. And infections occurring more than 48 hours after admission are usually considered nosocomial (WHO, 2002).

1.2.2 Hospital: This systematic review especially focuses on healthcare acquired infections that were gained during medical care in hospitals, which is also known as nosocomial infections. Here hospitals can range from highly equipped hospitals/clinics and technologically advanced university hospitals to front-line units with only basic facilities.

1.2.3 Infrastructure: Infrastructure is broadly defined as the physical and organizational structures which are important to support the operation of a society. In here, the hospital infrastructure is defined as the physical construction and engineering of the hospital building and its internal furnishing and settings. Besides, the dynamic construction or renovation process of hospitals is known also to result in HAI but is considered beyond the scope of this review. *Healthy* infrastructure here means the infrastructure which potentially has a positive role for people's health.

1.2.4 Abbreviations: A list of abbreviations used throughout this dissertation can be found in Appendix 1.

1.3 Causes and risk factors of healthcare acquired infections

The causes of HAIs could be all kinds of microorganisms, such as virus, bacteria, fungus and so on (Wenzel, 1997). A range of factors promote infection among hospitalized patients, including high density of pathogens and population in hospital, vulnerability and compromised immunity of patients, poor hygiene and insufficient cleaning, extensive use of broad-spectrum antibiotics, increasing variety of medical procedures and invasive techniques creating potential routes of infection and so forth (WHO, 2002). The WHO study, and others, has also shown that the highest prevalence of HAIs occurs in intensive care units and in acute surgical and orthopaedic wards. Infection rates are higher among patients with increased susceptibility because of old age, underlying disease, or chemotherapy.

1.4 Main types of healthcare acquired infections

The most common types of HAIs are surgical site infections, urinary tract infections and lower respiratory tract infections (WHO 2002). However, there might be country difference. For example, in Europe the most frequent HAIs are urinary infections, followed by respiratory tract infections, surgical site infections and others (HELICS, 2006). While the UK reported gastro-intestinal infections as the second frequent infection as HAI following the surgical wound infections (UK Hospital Infection Society, 2006).

To be more specific, the nosocomial respiratory infections often present themselves as ventilator associated pneumonia (VAP), and are often caused by acinetobacter baumannii and other gram negative rods, Legionella, aspergillus, mycobacterium tuberculosis, hospital-acquired pneumonia etc. The common pathogens contributing to gastro-intestinal infections include rota- and

norovirus, and clostridium difficile (C. difficile); while E. coli and other gram negative rods and enterococci cause urinary infections and pseudomonas aeruginosa (PSAE) and staphylococccus aureus cause skin infections. Besides, some pathogens can contribute to other types of HAIs or multiple infections, such as Candida albicans which causes opportunistic oral and genital infections, and stenotrophomonas maltophilia which contributes to both respiratory and urinary infections (Coffin & Zaoutis, 2005).

The inappropriate use of antibiotics and increase of drug-resistant or multidrug-resistant organisms raise the risk of HAIs as well. Burke (2003) pointed out that approximately 70% of HAIs are caused by drug-resistant strains of bacteria. And staphylococci, pneumococci, and enterococci present some of the most severe problems with drug resistance (Knobler et al., 2003) although there are geographical variations.

1.5 Main sources and transmission routes of healthcare acquired infections

The main sources of hospital infections can be categorized as environmental source (air, water, architecture), patient-related source (degree of illness or immunity, age, length of hospital stay), and iatrogenic source (surgery or invasive procedures, equipment and devices, and antibiotic use) (Alexander, 2007).

The architecture factor is directly related to environmental source of healthcare acquired infections, thus the main environmental transmission routes of the infections are summarised here. In general, hospital-acquired infections are transmitted via three environmental routes—air, surface contact, and water (Sehulster et al., 2003).

1.5.1 Airborne transmission: Droplets and droplet nuclei of microorganisms can be transmitted in the air, causing infection in patients either in direct or indirect way (through contamination of equipment or devices) (Sehulster et al., 2003).

Microorganisms that causes airborne HAIs include respiratory viruses (such as influenza and measles that do not carry far from the source, or tuberculosis and varicella zoster that may spread over long distance) (WHO, 2002), bacteria (which are mainly gram-positive cocci from the skin) (Weinstein, 2004), and fungal spore (the most common is Aspergillus which carried through dusts in the air) (Perdelli et al., 2006).

1.5.2 Surface contact transmission: Although airborne transmission poses severe risk of HAIs, contact contamination via direct person-to-person, and indirect environmental surfaces and other reservoirs are considered as the major transmission route of infections acquired in hospital (Bauer et al., 1990). Healthcare workers' hands play a key role in contact-spread transmission (Ulrich & Wilson, 2006), and it is well established that hand washing and hygiene is the single most important measure to prevent the spread of pathogens in hospital (Boyce & Pittet, 2002). The microorganisms that transmitted by surface contact are mainly bacteria, such as MRSA, VRE, and *C. difficile* (IOM, 2004).

1.5.3 Waterborne transmission: Water as a reservoir for microorganisms can be an important route for HAIs. Hospital water supply systems providing tap water from faucet and bath water can be contaminated if not properly disinfected. Bacteria, viruses, and fungi all accounts for waterborne diseases, with viruses as only a small percentage (Clark & John, 2006). Gram-negative bacteria *Pseudomonas aeruginosa* is identified as the most common pathogen in tap water (Reuter et al., 2002). *Legionella* is another pathogen commonly found in tap and bath water, and the highest concentration of *Legionella* are found to colonize in water distribution systems such as cooling towers, hot water storage, and condensers (Noskin & Peterson, 2001).

1.6 Relationship between infrastructure and healthcare acquired infections

The hospital infrastructure is, as said before, closely related to environmental transmission of nosocomial diseases. On one side, hospital infrastructure are primarily taken as safe for patients and healthcare workers, however, emerging

evidences of HAI cases and outbreaks show a causal relationship traced back to harmful infrastructure after laboratory confirmation or epidemiology investigation, thus putting patients or staff at risk (Bartley & Olmsted, 2009). On the other side, it seems apparent that infection control measures can be supported by modern hospital design and architecture, such as offering sufficient space or isolation room to treat patients properly, and there are increasingly studies focusing on healthy infrastructure to prevent HAIs.

Hospital infrastructure and facilities vary worldwide, with both negative and positive influences reported. However, common facts and principles regarding relationship between infrastructure and HAIs can be merged into four themes according to transmission routes as summarised below.

1.6.1 Infrastructure and airborne transmission

Many studies pointed out a detrimental role of improper ventilation systems in airborne transmission, and conversely good designed ventilation could potentially prevent HAIs transmitted by air. Li et al.'s review (2007) on the relationship between building ventilation and transmission of airborne infection concluded a strong evidence of such adverse association contributing to spread of measles, influenza, chickenpox, smallpox, tuberculosis and severe acute respiratory syndrome (SARS). However, they also concluded lack of sufficient data to specify the minimum ventilation requirements in relation to prevent spread of airborne infectious diseases. Tang et al.'s report (2006) on ventilation control and airborne infection in healthcare settings described the generation, transmission and inhabitation process of infectious aerosol, and suggested use of negative pressure ventilation systems to control airborne transmissions.

Some other studies also illustrated that the contamination or malfunction of ventilation systems and lack of cleaning and maintenance gave rise to HAIs. The association between contamination of ventilation systems and nosocomial disease outbreaks are especially commonly cited. For example, Kumari et al. (2006) found the ventilation grilles in two patient bays harboring MRSA contributed to one MSRA outbreak, Lutz et al., (2003) determined an outbreak of

invasive *Aspergillus* infection in surgical patients to be associated with a contaminated air-handling system, while McDonald et al. (1998) found contaminated air conditioners associated with an outbreak of Acinetobacter spp. bloodstream infections in a nursery. With regard to malfunctioning, Yavuz et al. (2006) found plenum ventilation together with malfunctioned automatic doors of operating theater independently put patients at higher risk of sternal surgical site infections compared with laminar-flow ventilation systems with normally functioning automatic doors.

In addition, some studies identified hospital construction and renovation activities that generated dusts or particulates being the sources of airborne nosocomial disease outbreaks, for example, Oren et al. (2004) conducted a study during extensive hospital construction and renovation and found an outbreak of invasive pulmonary aspergillosis soared to a 50% infection rate among acute leukemia patients in wards with natural ventilation. Thus interventions such as positive pressure ventilation systems, High Efficiency Particulate Air filter (HEPA filter), installation of barriers, and windows closing etc. were recommended (Humphreys et al., 1991; Iwen, Davis, Reed, Winfield, & Hinrichs, 1994; Loo et al., 1996; Opal et al., 1986; Oren, Haddad, Finkelstein, & Rowe, 2001).

1.6.2 Infrastructure and contact transmission

Hand washing, as mentioned before, is the single most important measure to prevent contact transmission of pathogens in hospital. However, hand compliance rate is commonly studied as low and the frequency of hand washing by personnel is influenced by the accessibility of hand hygiene facilities (Kaplan & McGuckin, 1986; Freeman, 1996; Bischoff et al., 2000). Thus the location and availability of hand washing facilities such as sinks for traditional soap and water, and dispensers for alcohol-based hand-rub play a key role for preventing contact route transmission of HAIs.

As the CDC/HICPAC guidelines recommend alcohol-based hand-rubs as the standard for hand hygiene practices in healthcare settings (Boyce & Pittet, 2002), the dispensers for hand rubs seem working better than traditional sinks, not only

because of the hand-rubs, but also because they do not require plumbing and can be made adjacent to healthcare workers working place and patient's bed and at many other locations in hospital (Boyce & Pittet, 2002). However, dispenser systems should be checked and evaluated regularly as the malfunction of dispensers could discourage use by personnel when they are blocked or partially blocked or they do not deliver the product appropriately either for the amount or the way (sometimes the product squirted onto the wall instead of the caregiver's hand.) (Kohan et al., 2002).

Besides, several studies showed furnishing or building material of a hospital could potentially be the risk of contact-spread HAIs as well. Some studies defined carpeting as susceptible to be contaminated by bacteria and fungi (Anderson et al., 1982; Skoutelis et al., 1994; Beyer & Belsito, 2000; Boyce et al., 1997). While Lankford et al. (2006) compared the performance of different wall finishes in the hospital and reported different level of VRE harboring and capability of transferring the pathogen via hand contact. However, there is no conclusive statement of the association between building or furnishing materials and HAIs, and the CDC/HICPAC guidelines do not recommend against the use of carpeting or upholstery in the hospital, except carpet use for areas where patients are at high risk of airborne diseases or where spills are likely to happen, and upholstery use in areas housing immunocompromised patients (Sehulster et al., 2004). White (2006) also suggested that carpet is impropriate in isolation rooms or around sinks for in soiled areas.

1.6.3 Infrastructure and waterborne transmission

Hospital water supplying infrastructure such as sinks, faucets, showers and toilets were studied to be potential reservoirs for microorganisms (Blanc et al., 2004; Conger et al., 2004; Mineshita et al., 2005; Squier et al., 2000). These fixtures produce aerosols that can carry and disperse pathogenic microbes, and their wet surfaces facilitate the proliferation of molds and other microorganisms. Stout et al. (1998) found that a properly maintained copper-silver ionization system was more effective in reducing the recovery of *Legionella* than the superheat-and-flush method for the hospital water distribution system. However, there is still limited evidence linking the water infrastructure to HAIs, and no

consensus has been reached regarding the removal or disinfection of these fixtures for general use (Sehulster et al., 2004).

While Rogers' review (2006) on decorative fountains in healthcare environments found no evidence linking the placement of a water fountain in hospitals to waterborne HAIs, Thomas et al. (2012) observed an outbreak of legionnaires disease associated with exposure to a decorative fountain located in a hospital public area. And the AIA guideline (2006) also recommended no fountains be installed in enclosed spaces in hospitals.

1.6.4 Infrastructure and multiple routes transmission

The design of patient rooms in a hospital is considered to be related to multiple transmission routes of HAIs, especially for airborne and contact-spread infections. Multi-occupied rooms (usually together with less space per patient and more people for toilet sharing) in hospital are identified to be contributing to higher risk of HAIs, compared with single rooms. The investigation of these hospitals found a scarcity of single rooms with private toilets as key factors that prevented patients from timely isolation and gave rise of the spread of *C. difficile* as well as prolonged duration and high mortality of the outbreaks (Healthcare Commission, 2006, 2007). Korpela et al. (1995) identified the transfer of *Shigella* spp. between two patients sharing patient room and toilet in a ward and emphasized the importance of isolation in hospital settings. On the other side, several reviews supported the link between single rooms in hospitals and reduced HAI rates, including Chaudhury et al.'s review (2005) on the single- versus multi-bed rooms, and Calkins and Cassella's study (2007) concluding that private bedrooms reduce the risk of infection and convey a major safety advantage in nursing homes compared to shared bedrooms.

Besides the facility differences between single- and multi-bed rooms, other facts also play accumulative effects contributing to risks of HAIs. For example, in some countries, when one patient is discharged from a multi-bed room, cleaning staff are not allowed to clean the equipments or facilities attached to other patients remaining the room, thus increasing the risk of cross infection (Ulrich & Wilson,

2006). They also pointed out high proportion of single rooms in hospital enables separation of patients upon admission to prevent cross infections before diagnosis and any transmission of unrecognized carriers of pathogens.

1.7 Literature review regarding research question

1.7.1 Studies on the topic

Longstanding prevalence of healthcare acquired infections has lead to many studies. Studies relevant to this research question mainly focus on areas including:

- Epidemiological study investigating the outbreak of HAIs and its source traced back to infrastructure (Kumari et al., 2006; Lutz et al., 2003; McDonald et al., 1998; Oren et al., 2004; etc);
- Laboratory or microbiological study detecting the survival and proliferation of microorganisms on various hospital infrastructure (Lankford et al., 2006; Anderson et al., 1982; Harris, 2000; Noskin et al., 2000; Noyce et al., 2006; Modol et al., 2007; etc);
- Epidemiological study investigating the HAI rates before and after moving to a new or reconstructed hospital or unit (Preston et al., 1981; Goldmann et al., 1981; Huebner et al., 1989; Mullin et al., 1997; Smith et al., 1980; etc), or comparing between different hospital infrastructure design (Menzies et al., 2000; Larson et al., 1991; Drinka et al., 2003; Gastmeier et al., 2004; MacKenzie et al., 2007; etc).

A variety of hospital infrastructure were studied ranging from ventilation systems (Tang et al., 2006; Bouza et al., 2002; Jiang et al., 2003; etc), hand hygiene facilities (Lam et al., 2004; Kaplan & McGuckin, 1986; Bischoff et al., 2000; Larson et al., 1991; etc), building and furnishing materials (Harris, 2000; Noskin et al., 2000; Noyce et al., 2006; etc), copper-silver ionization system (Modol et al., 2007; Liu et al., 1994; Stout et al., 1998; etc), to single or shared

bedrooms and toilets (Gastmeier et al., 2004; Larson et al., 1985; Smith et al., 1980; Korpela et al. 1995; etc).

Existing studies have investigated the research question through difference perspectives and come up with some common findings. Firstly, the contamination of pathogenic microbes on hospital infrastructure is crucial. For example, Lankford et al. (2006) studied environmental surfaces in a hospital of 14 different materials, all harboring VREs and are capable to transfer the pathogen via hand contact. Secondly, improper and malfunction of hospital design can lead to HAI outbreaks (Kumari et al., 2006; Lutz et al., 2003; McDonald et al., 1998; etc). Third, well-designed and healthy infrastructure can reduce the rate of HAIs (Gordin et al., 2005; Larson et al., 1991; McManus et al., 1994; etc).

Among the existing studies which investigated the healthy infrastructure, all types of study design were used, such as quantitative studies (randomised controlled trial, cohort study, case-control study), descriptive studies, or merely inferences based on well-established theories, with varied reporting qualities. Furthermore, their focus of effectiveness of the healthy infrastructure involved both single and multiple infrastructure settings or interventions, careful examination will be needed for not equaling the effect of multifaceted intervention with its single aspect of the intervention. In a nutshell, there remains lack of rigorous assessment and evidence synthesis upon the effectiveness of all the kinds of healthy infrastructure for reducing noscomial infections, thus this systematic review is conducted to address this need.

1.7.2 Reviews on the topic

Several literature reviews have been conducted regarding the healthy hospital infrastructure and the prevention of HAIs, including:

- Hyttinen et al. (2011) explored the effectiveness of airborne infection isolation rooms, mainly regarding to minimise the potential for disease transmission.
- Beggs et al. (2008) explored the design of ventilation systems for hospital wards and other multi-bed rooms, and their effectiveness of removing airborne pathogens from ward spaces.
- Van de Glind et al. (2007) identified the benefits of single patient rooms for patients, using various outcome measures as hospital infection rates, privacy and dignity, noise and quality of sleep, patient satisfaction with care, recovery rates etc.
- Chaudhury et al. (2003) compared the advantages and disadvantages of single patient rooms versus multiple occupancy rooms in acute care environments, in the area of infection control and patient outcomes, staff efficiency, construction and operating cost, hospital management etc.
- O'Connell & Humphreys (2000) explored the intensive care unit (ICU) design and environmental factors to prevent the acquisition of infection.

Besides, three systematic reviews have as well been conducted related to the research question, including:

- Li et al. (2007) explored the association between the transmission of airborne infections and the ventilation of buildings. However, the setting was not restricted to hospitals, but all kinds of buildings such like offices, schools, churches, ships, aircrafts, and jails etc.
- Naikoba & Hayward (2001) studied the effectiveness of interventions aimed at increasing handwashing compliance among in healthcare workers. However, the interventions were not restricted to infrastructure such as automated sinks, but also involved various other methods like education, reminders, soaps and hand rubs, feedback of performance and so on.
- Dettenkofer et al. (2004) reviewed the evidence regarding the effects of hospital architecture and constructions on the occurrence of HAIs. However, the included studies contained not only single intervention, but

also multiple interventions, such as a move to other new premises or renovations, thus is unable to conclude whether the effect resulted from the multi-modal or any single intervention. Besides, the interventions regarding to ventilation, building and furnishing materials, and water system in hospital were not included in this review.

1.8 The rationale and reality for taking the systematic review

Systematic review has been increasingly used in the research of clinical medicine and healthcare. According to Mulrow (1994), systematic review can scientifically synthesise evidence from large databases, and evaluate the quality, generalisability and consistency of findings, thus advancing evidence-based interventions in practice. Compared to traditional narrative literature review, systematic review is more rigorous in study selection, assessment and integration (Hemingway et al., 2009).

According to the summary of the existing relevant reviews above, none of the literature reviews addressed the research question in full, nor did they assess the quality of the reviewed studies or report their exact findings. With regard to the existing systematic review, only the review by Dettenkofer et al. (2004) addressed in full the research question. However, this review did not consider the hospital constructions like ventilation, building materials, water system, and many included studies involved multi-modal interventions. Therefore, in order to bridge this gap and to identify the independent effect of the interventions, this systematic review is to systematically collate and synthesise the evidences of all kinds of hospital infrastructure and assess their real and independent effects regarding HAI prevention.

Especially, only healthy infrastructure which have positive effects for preventing HAIs will be reviewed, which is reasonable as there is ethical problem and scarcity of articles to prospectively study the infrastructure which might have a negative outcome for people's health. Besides, the focus of this systematic review is physical infrastructure only, since these permanent physical features could potentially prevent HAIs without the need for ongoing staff training, reminders,

or audits. Finances spent on physical infrastructure may be more efficient than finances spent on changing attitude and behaviour of health workers and changing hospital culture. In addition, there are several guidelines for hospital construction and design, for example, the American Institute of Architects (AIA) published the updated 2010 edition of "Guidelines for Design and Construction of Hospital and Healthvare Facilities" (AIA, 2010), which is widely referred to by hospitals in the US and other countries, but still no transparent systematic review of empirical evidence has been published in this field.

CHAPTER 2: AIM AND OBJECTIVES

AIM

The aim of this review is to synthesise evidence to assess the effectiveness of various hospital infrastructure in preventing healthcare acquired infections (HAI), and to provide evidence for hospital construction or renovation and guideline making in regard to reducing HAI.

OBJECTIVES

1. To collect and synthesise evidences of all the kinds of infrastructure that were studied to be effective in prevention of HAIs:

- To collect and extract the studies associated with hospital infrastructure design and construction that resists healthcare acquired infections based on the set criteria.
- To synthesize the data and to integrate the evidences into categories.

2. To evaluate both the quality and effect of the healthy infrastructure for preventing HAIs.

- To assess the quality of included studies to see how trustable are these evidences.
- To discuss the findings of included studies and assess their effects to see how strong are these evidences.

3. To synthesise data to see how much percentage could infrastructure play in reduction of HAIs, and to discuss and provide evidence-based strategies for implementing healthy infrastructure to prevent HAI in practice.

CHAPTER 3: RESEARCH METHODOLOGY

3.1 General framework of the systematic review

This study followed the standard procedure for doing a systematic review (Centre for Reviews and Dissemination, 2009). To ensure the relevance of study, a systematic research for literature on healthy hospital infrastructure to prevent HAIs was conducted, followed by a screening and review of eligible studies. Then the eligible studies were categorised by the infrastructure type, and under each group, data extraction and quality assessment of the studies were conducted using several tools, with the purpose of prioritising the most relevant fields for further analysis.

In data synthesis under each infrastructure type, a strategy of triangle was applied to synthesise results of studies using different method of data collection (Bryman, 2009). Data from studies using different study design were integrated, and the bias or weakness of any of the methods can be compensated for by the strengths of another, thus increasing the reliability and validity of the results (Bryman, 2009).

In addition, through ethical issue is less concerned in this study because the review is based on secondary data, the main ethical problem may occur in the

searching process. Because of the deficiency of the search strategy such as limited databases, some relevant publications or valuable studies may be missed. Moreover, it may be difficult to access to some literature such like paid-for publications. Besides, only the author herself conducted the whole searching and selection, some relevant articles might be missed due to the author's occasional inappropriate performance in the selection process against the selection criteria.

3.2 Searching process

A search strategy was developed for identification of relevant studies. An outline of search strategy was illustrated in Appendix 2.

All main electronic databases in the field of medicine or public health were searched. Database included Medline, PscyINFO, and Embase. Advance searches were used with keywords which were mapped to subject heading (search terms). Key words were defined from the review question, such as intervention and outcome. There was no need to define the population and setting. For an exhausted searching, key words of study design were not defined in the initial stage. It was due to the fact that some studies met the criteria for the study design, but they did not state them in the title or abstract. Furthermore, search terms were complemented with index terms provided by different electronic databases.

Further Limits were set to English language and publication year (1980 to present). The search history based on the three databases was shown in Appendix 3a, 3b, and 3c respectively.

An ancestry search for reference lists of relevant articles was checked by hand to identify additional studies. Google scholar search engine was used as supportive source to locate the potentially useful articles. However, 'Grey literature' including unpublished information and conference proceedings will not be searched due to non-availability or difficulty of access to these literatures. After

initial identification of studies, a further screening of title, abstract, and full text of each study was conducted.

3.3 Selection criteria for eligible studies

Articles identified in the initial search were selected to meet the inclusion criteria, in the order of title, abstract, and full text of studies. Given the research question of this systematic review, the selection criteria were developed as follows, including types of study, intervention, outcome, population and setting etc. A table of inclusion and exclusion criteria for study selection was outlined in Appendix 4.

3.3.1 Types of studies: Criteria on study design were set based on system used by the UK National Health Service (NHS) for ranking the quality of evidence, see Appendix 5. Level A and Level B which include RCT, cohort study (both prospective and retrospective), and case control studies will be selected. In addition, a quasi-experimental design involving a control group without randomisation was also included, as it is just second to RCT regarding strength of evidence. Only these research designs were selected because they are more powerful in testing effectiveness of the intervention, and provide more valid and trustable research results.

3.3.2 Types of interventions: The intervention could be any single infrastructure intervention in the hospital. Actually there are many studies about multi-modal interventions which are very common as construction or renovation of a hospital usually results in multiple changes in personnel, space, facilities at the same time. However, these studies were excluded as it is impossible to distinguish the effect of single intervention from other confounding factors.

The comparison could be either no infrastructure implementation or any traditional infrastructure implementation, which is different from the healthy infrastructure under the same purpose.

3.3.3 Types of outcome measures: The study outcome should be clearly and directly measured in terms of infection rates, preferably reported as relative risk (RR) with a 95% confidence interval (95%CI) comparing the healthy infrastructure with the other infrastructure as comparator. Studies with indirect outcomes as reduction of microbe counts or growth of health behaviour compliance were excluded as these may not necessarily turn into a reduction of healthcare acquired infection. Besides, the studies may have different follow-up times or may use different methods for verification of infection, such as diagnosis confirmed or self-reported, no limitation was made on these.

3.3.4 Types of population and the setting: There is no need to set criteria for population and the setting, as the articles on healthcare acquired infections necessarily studied the population in the hospital as well as within the hospital setting. Besides, no restriction will be placed on participants' age, nationality, ethnical background etc.

3.3.5 Publication limits: Articles published in from 1980 onwards and published in English language will be included for further analysis.

3.4 The screening process of identification of eligible studies

The inclusion and exclusion criteria were developed and used to assess each study. A two-stage screening was conducted to systematically narrow down the potential studies, so as to ensure the credibility of the review (Centre for Reviews and Dissemination, 2009). The first stage of screening was to focus on the title and abstract of the articles. Studies included in this round of filtering had to merely focus on single hospital infrastructure intervention/design; be the appropriate study type previously mentioned (RCT, cohort study, case control study, or quasi-experimental study); measure the outcome in terms of HAI rates; and be written in the English language and published from 1980.

Then, a second stage of screening was conducted by reading the main body of articles. The inclusion criteria are the same as the first round of filtering, and it is

taken when the necessary information related to the inclusion criteria cannot be identified in the first stage. For example, many studies did not mention whether it is a single- or multi-modal intervention in the abstract, and sometimes the study design or outcome measure is unclear in the abstract as well.

The selection is performed by the author herself. A detailed process of screening with numbers of studies selected in each stage was illustrated in Appendix 6.

3.5 Quality assessment of included studies

As mentioned before, three types of study design are considered eligible to be included for this systematic review, which are RCT, cohort study, case control study, and quasi-experimental study. These types of study design are ranked high in study design hierarchy as they are more powerful for providing evidence of causality (see Appendix 5). According to Bryman (2009), the key point of quality assessment is the evaluation on validity and reliability of data collection and analysis. Existing checklists produced by the Critical Appraisal Skills Programme (CASP) for quality assessment of the studies were used (Public Health Resource Unit, 2006). For the studies with RCT and quasi-experimental design, the CASP RCT checklist was used (see Appendix 7). The only difference between quasi-experimental design and RCT design is randomization and allocation concealment, when there is no separate checklist for quality assessment of quasi-experimental study, the same criteria of assessment for RCT study can also be used to assess quasi-experimental studies (Centre for Reviews and Dissemination, 2001). For the studies with cohort study design, the cohort study checklist was used (see Appendix 8). There turned out to be no case control study meeting the inclusion criteria according to the screening results in the later stage.

Each of the studies was evaluated against each question of the checklist. The quality was judged as 'Yes' if adequate and clear, was judged as 'No' if having potential for bias, and was judged as unclear if necessary details were not provided. Detailed information was provided following each judgment.

3.6 Extraction of study data

Data were extracted from included studies to reduce a complex trial into a matrix of categories and numbers (Orwin 1994), for facilitating following data analysis. The data extraction form followed the broad format of PICOCS to incorporate diversity of data (CRD, 2009), and was based on a list of study characteristics as follows. A table of study characteristics was also outlined in Appendix 9.

- Study design
- Population and setting (country, hospital setting, participants, sample size, age and gender, length of stay in the hospital).
- Intervention and control (type of hospital infrastructure, intervention, comparator).
- Outcome (type of HAIs measured, follow-up time, main findings as change of infection rates, and conclusion).

The selection of the study characteristics was partly guided by earlier reviews (Dettenkofer et al., 2004), and partly based on common information emerged in the studies. To ensure the reliability of the data extracted, the author read the full text of each included study for several times, and a pilot test for data extraction sheet was performed (CRD, 2009).

3.7 Data synthesis

Generally, two steps were performed for data synthesis: 1. Synthesis of data under each hospital infrastructure category; 2. Aggregative synthesis of data in a triangulation for all healthy hospital infrastructure for reducing HAIs.

Under each infrastructure category, variables in each study were grouped and systematically summarized to observe the similarities and differences. Variables mainly included study design and hospital setting, intervention, comparison, and

outcome. If available, the RR of infection rates with 95% CI for each study will be especially emphasized to see the individual effect size. For studies where RR was not reported, other forms of outcome presentation such as attributive risk will be synthesized. Furthermore, for comparable studies, meta-analysis will be used in order to combine the outcomes of comparable studies and give a weighted estimate of pooled RR and 95%CI. However, if there is no comparable studies, narrative synthesis will be employed to see whether the implementation of that infrastructure is effective for reducing relevant HAIs.

In the triangulation part, evidences under each hospital infrastructure category were combined and triangulated, focusing on the effectiveness of healthy hospital infrastructure in decreasing HAI rates as a whole.

CHAPTER 4: STUDY RESULTS

4.1 Study selection

Initially, a total of 1717 relevant articles were identified through the search of three academic databases. Through ancestry search for the reference lists, an additional 27 articles were produced. After applying the mentioned selection criteria, 10 final articles were included for the review. The selection process was outlined by using the PRISMA flow chart (Moher et al., 2009) in Appendix 6.

The 10 included studies that met the selection criteria involved three types of hospital infrastructure. Two of them studied handwashing facilities (Barrera et al., 2011; Swoboda et al., 2004), six of them studied patient rooms mainly focusing on single- versus multi-rooms (Bracco et al., 2007; Cheng et al., 2010; Drinka et al., 2003; Kibbler et al., 1998; Larson et al., 1985; mcManus et al., 1985), and the other two studied the copper-silver ionization system for water supplying facility (Modol et al., 2007; Stout et al. 1998). A table of the 10 included studies is available in Appendix 10. For the following quality assessment, data extraction for study characteristics, and data synthesis, the analysis of the three

types of infrastructure was conducted separately at the first stage, and was integrated and triangulated for a whole idea at the second stage.

Besides, it is worth mentioning that no study met the selection criteria for the important hospital infrastructure such as building and furnishing materials in hospital. However, a literature review of these types of hospital infrastructure was conducted and presented in the Discussion part to give a brief idea of these infrastructure types regarding prevention of nosocomial infections.

4.2 Reasons for excluded studies

Out of the 1744 articles identified from the primary search, 83 papers were screened at the abstract and full-text stage and 73 papers were excluded. The reasons for exclusion are mainly: 1. Other study design rather than the mentioned criteria; 2. Laboratory study for microorganisms only without measuring the HAI rates; 3. Only studied the health behaviour compliance without measuring the HAI rates; 4. Multifaceted intervention/design rather than single intervention/design; 5. The major intervention is not the same as the one mentioned in the title or abstract; 6. Cannot access to the full text but only abstract was available.

Brief summary of the excluded studies and reasons for exclusion was illustrated in Appendix 11.

4.3 Quality assessment of included studies

As mentioned before, the CASP checklists for quality assessment of different studies were used. The result and detailed argument on quality of studies according to each criterion is illustrated in Appendix 12.

4.3.1 Quality assessment of studies on handwashing infrastructure

The two included studies used different study design, which were quasi-experimental study (Swoboda et al., 2004) and prospective cohort study (Barrera et al., 2011) respectively. For recruitment of participants, it was more appropriate for Swoboda et al. (2004) to only recruit patients with a length of stay more than 48 hours after admission, rather than to consider all patients as did by Barrera et al. (2011), because as defined by WHO (2002) infections occurring more than 48 hours after admission are usually considered nosocomial.

Both of the studies described in detail the characteristics of the participants, such as age, gender, length of stay, and other relevant facts. For outcome measure, Swoboda et al. (2004) generally reported more details regarding to the process of measurement, for example, it mentioned all the participants were measured against the HAIs with no loss to follow-up, and personnel detecting the infections were blinded to their status of whether they were from intervention or comparison group. However, Barrera et al. (2011) failed to report such information.

For confounding factors, both of the studies identified the potential confounding variables according to their own study settings, and used statistical model to analyse them. Swoboda et al. (2004) identified and analysed the important confounding variables such as patient co-morbidities, patients isolation status, and use of antimicrobials within 48 hours of IMC admission using Logistic regression model. Barrera et al. (2011) also identified potential risk factors as device utilities, nurse-to-patient ratios, personnel work experience, and used multivariate risk factor analysis model. However, Barrera et al. (2011) failed to consider antimicrobials use as a potential important risk factor for HAI rates.

For presentation of results, both of them used attributive risk fraction, but only Swoboda et al. (2004) provided the odds ratio (OR) with 95% confidence interval (95%CI), which was more precise and clear. Besides, only Swoboda et al. (2004) discussed the generalisability of the study results.

4.3.2 Quality assessment of studies on patient rooms

All the four included studies on patient rooms used cohort study design to address the question, two studied prospectively (Bracco et al., 2007; Larson et al., 1985) and two studied retrospectively (Ben-Abraham et al., 2002; McManus et al., 1994). For participants recruitment, only Bracco et al. (2007) and Ben-Abraham et al. (2002) reported the details of recruitment process, and both of them recruited patients with more than 48 hours length of stay in the hospital, which were appropriate as infections occurred after 48 hours in the hospital are usually considered as nosocomial (WHO, 2002).

All the studies described the characteristics of the participants, but Ben-Abraham et al. (2002) and McManus et al. (1994) did not report gender distribution, and Larson et al. (1985) failed to report both gender and age compositions of the participants. All the studies mentioned detailed information regarding outcome measurement, and all of them used consistent method for HAI identification throughout the study to minimize bias.

Except McManus et al. (1994), the other three studies identified thoroughly potential confounding factors according to their own settings, while McManus et al. (1994) only mentioned burn percentage of body surface as potential confounder, and ignored other important factors such as nurse-to-patient ratio, use of antibiotics, clinical practice and so on. All the four studies considered the confounders in the study design or analysis, where Bracco et al. (2007) conducted nominal logistic regression for multivariate analysis of the confounding factors, while the other three studies compared the confounders in the intervention and comparison group and found they were similar distributed. None of the studies reported loss to follow-up rate. All the studies seemed to have long enough study period for the cohort (ranging from 2.5 years to 20 years), except Ben-Abraham et al. (2002) which performed 6 months for both intervention and comparison group and seemed not long enough compared to the other studies.

For presentation of results, Bracco et al. (2007) reported the main result as relative risk with p-value, and the other three studies reported the result as attributive risk with p-value. None of the studies reported 95% confidence

interval, and were thus not quite precise in result presentation. Besides, none of the studies discussed the generalisability of the study results.

4.3.3 Quality assessment of studies on copper-silver ionization system

Two studies met the inclusion criteria for this review (Modol et al., 2007; Stout et al., 1998), both used prospective cohort study design. For recruitment of participants, Stout et al. (1998) appropriately recruited pneumonia patients who developed symptoms 48 hours after admission for detection of nosocomial Legionella disease, which was preferable as disease developed 48 hours after hospital admission which was usually considered nosocomial according to WHO (2002). However, Modol et al. (2007) failed to report the recruitment details.

Both of the studies failed to describe in detail the characteristics of the participants, such as age, gender, length of stay, and other relevant facts. And both of them did not report the process of outcome measure, missing the information such as blinding or loss to follow-up rate. Furthermore, both of the studies did not consider confounding factors which could potentially influence nosocomial Legionella incidence in spite of the copper-silver ionization system or traditional disinfection method for hospital water supply system, such as patient isolation status, recent use of antimicrobials, or nurse-to-patient ratios etc.

For presentation of results, Modol et al. (2007) reported as change in nosocomial Legionella incidence between intervention and comparison group, while Stout et al. (1998) presented a change in average noscomial Legionella cases per year between intervention and comparator. Both of them did not report relative risk with 95% confidence interval, thus were not very precise in result presentation. Besides, both of them did not mention or discuss the generalisability of the study results.

4.3.4 Quality assessment of studies on ventilation system

Both of the two included studies (Brandt et al., 2008; Jiang et al., 2003) investigating ventilation system in hospital used prospective cohort study design. Both of the studies did not mention in detail the recruitment process, thus it is not possible to identify whether there was any recruitment bias. And both of them failed to report the characteristics of the participants, such as age, gender, length of stay and so on. For outcome measure, Brandt et al. (2008) reported the definition and methods for indentifying HAIs in the study which was severe surgical site infection (SSI); while Jiang et al. (2003) did not report such information and it was unclear whether there was any bias in measuring infections.

For confounding factors, Brandt et al. (2008) identified potential confounding factors from both hospital-based and patient-based perspectives, and performed multivariate analysis for assessing these confounders; while Jiang et al. (2003) failed to consider any potential confounders in the study design and analysis.

Neither of the studies reported loss to follow-up rate. For the length of study period, Brandt et al. (2008) used 4-year retrospective data which seemed long enough. Although Jiang et al. (2003) only used 2 months retrospective data, but as they were exploring SARS outbreaks which was irregular and only happened during that period, and the sample size of 431 is somewhat big, it is considered as acceptable here. With regard to outcome presentation, Brandt et al. (2008) used adjusted odds ratio with 95% confidence interval, which is more precise than Jiang et al. (2003) who reported the outcome as infection rate of each study group with relevant p-values. In addition, Brandt et al. (2008) mentioned generalisability of the study results and assumed further discussion was required, while Jiang et al. (2003) did not discuss the issue of generalisability of the study findings.

4.3.5 Triangulation of study quality of all included studies

Compared to the excluded studies, all the ten included studies made good attempts in research design and data analysis. The only quasi-experimental study (Swoboda et al., 2004) fulfilled 6 out of the 10 quality assessment criteria

for RCT design. Despite of the two criteria (criterion 2 and 3) which is inappropriate for quasi-experimental study, and criteria 8 which is not a question of "Yes" or "No", the study actually fulfilled 6 of 7 criteria, only failed to have enough participants to minimise the play of chance, thus is of very high quality. For the other nine cohort studies, there are 12 CASP criteria for their quality assessment, in spite of criterion 8 which is again not a question of "Yes" or "No", they fulfilled from 4 to 8 out of the 11 criteria, with a great variation in quality. It is worth mentioning that for criterion 6 and 7, the studies which satisfied both 6A and 6B (or both 7A and 7B) were classified as meeting the criteria 6 or 7.

The cohort studies which did not meet the majority of the criteria were included for analysis because they were potentially valuable even though they had some defects in study quality. Exclusion of such studies might lead to the miss or insufficiency of information in data analysis and conclusion. Table 1 outlines the overview of the results of quality assessment. Detailed arguments for quality assessment of each study are available in Appendix 12.

Table 1. Overview of the results of quality assessment of the included studies (one quasi-experimental study and nine prospective cohort studies)

CASP checklist of 10 questions for quality assessment of a randomised controlled trial	**Swoboda et al. 2004**	**CASP checklist of 12 questions for quality assessment of a cohort study**	**Barrera et al. 2011**	**Bracco et al. 2007**	**Larson et al. 1985**	**Ben-Abraham et al. 2002**	**McManus et al. 1994**	**Modol et al. 2007**	**Stout et al. 1998**	**Brandt et al. 2008**	**Jiang et al. 2003**
1. Did the study ask a clearly-focused question?	√	1. Did the study address a clearly focused issue?	√	√	√	√	√	√	√	√	√
2. Was this a randomised controlled trial (RCT) and was it appropriately so?		2. Did the authors use an appropriate method to answer their question?	√	√	√	√	√	√	√	√	√
3. Were participants appropriately allocated to intervention and control groups?		3. Was the cohort recruited in an acceptable way?		√		√					√
4. Were participants, staff and study personnel 'blind' to participants' study group?	√	4. Was the exposure accurately measured to minimize bias?	√	√	√	√	√	√	√	√	√
5. Were all of the participants who entered the trial accounted for at its conclusion	√	5. Was the outcome accurately measured to minimize bias?		√	√	√	√			√	
6. Were the participants in all groups followed up and data	√	6A. Have the authors identified all important		√	√	√				√	

collected in the same way?		confounding factors? 6B. Have they taken account of the confounding factors in the design and/or analysis?	√	√	√	√	√			√	
t7. Did the study have enough participants to minimise the play of chance?		7A. Was the follow up of subjects complete enough? 7B. Was the follow up of subjects long enough?	√	√	√		√	√	√	√	√
8. How are the results presented and what is the main result?	NA	8. What are the results of this study?	NA	NA	NA	NA	NA	NA	NA	NA	NA
9. How precise are these results?	√	9. How precise are the results? And how precise is the estimate of the risk?								√	
10. Were all important outcomes considered so the results can be applied?	√	10. Do you believe the results?		√	√		√			√	
		11. Can the results be applied to the local population?									
		12. Do the results of this study fit with other available evidence?	√	√	√	√	√	√	√		√

(1) General advantages of study quality

Generally speaking, each of the ten studies was conducted with a clear aim of evaluation the effectiveness of the specific infrastructure for reduction of HAIs. And the chosen study designs were appropriate for answering their research question. In addition, the exposure in each study, which was different infrastructure, was all accurately measured without bias due to the fact that unlike other non-physical exposure which needs to be verified and controlled, the physical infrastructure is in its nature easier to measure.

(2) Recruitment

As guided by WHO (2002), infections occurring more than 48 hours after admission are usually considered nosocomial. Infections detected shorter than this period might be acquired from other previous occasions, such as acquired from community but in an incubation period when admitted to the hospital, and developed symptoms thereafter. Thus it is more appropriated to recruit participants who had a length of stay (LOS) in the hospital for more than 48 hours after admission. Of the ten included studies, nine studies recruited patients as participants and therefore were expected to use the 48 hours criteria. However, only three studies (Swoboda et al., 2004; Bracco et al. 2007; Ben-Abraham et al., 2002) mentioned clearly in the article that only participants with more than 48 hours LOS were recruited, the other six studies either recruited all participants in the unit or failed to report the recruitment information.

The other one study recruited healthcare workers as participant (Jiang et al., 2003), thus did not need to fit with the 48 hours criteria. In this study, the healthcare workers who worked for the SAS patients were recruited, and was deemed as appropriate.

(3) Confounding factors

Many factors other than the exposure of the intervention infrastructure could contribute to the increase or decrease of HAI rates, such as important conditions of patients (comorbid illness, surgery types, device utilities), nurse-to-patient ratio, work experience of healthcare personnel, recent antibiotics use, isolation status. Therefore it is critical for the studies to identify all potential confounding factors, balance them in the study design or examine their effect if these factors were different between the intervention and comparison group, such as analysing their independent risks for the outcome of HAIs using statistical models.

Out of the ten included studies, the quasi-experimental study (Swoboda et al., 2004) and four cohort studies (Bracco et al., 2007; Larson et al., 1985; Ben-Abraham et al., 2002; Brandt et al., 2008) identified all potential confounding

factors based on their local study settings, and in the meanwhile considered these confounders in the study design or analysis. Two studies (Barrera et al., 2011; McManus et al., 1994) identified partially the confounders and considered them the study design or analysis, while the rest three studies (Modol et al., 2007; Stout et al., 1998; Jiang et al. 2003) failed to include any information about confounding factors in the articles.

(4) Process of outcome measure

For outcome measurement, which is measure of HAI rate, four of the nine cohort studies failed to provide detailed information about the process of how the HAIs were monitored and validated (Barrera et al., 2011; Modol et al., 2007; Stout et al., 1998; Jiang et al., 2003), thus it was unable to assess if there was any bias for the measurement in these studies. For the quasi-experimental study (Swoboda et al., 2004), it was mentioned that the participants in all groups were followed up and data collected in the same way by the review committee, and was thus deemed as qualified for outcome measure. The nine cohort studies all did not mention the information about loss to follow-up rate, it was therefore unable to judge whether any bias was related to this.

For follow-up time, the nine included cohort studies ranged from 2 months to 10 years. The only two studies which had study duration less than 1 year were Ben-Abraham et al. (2002) as 6 months and Jiang et al. (2003) as 2 months. However, the study period of 2 months for Jiang et al. (2003) was reasonable as the study was based on a SARS outbreak which was short and only occurred during that period. For the quasi-experimental study (Swoboda et al., 2004), rather than asking about follow-up time, the correspondent criterion was asked as whether it had enough participants for minimizing bias. It was good that Swoboda et al. (2004) conducted power calculation for sample size and identified the minimum participants needed to avoid bias, however, the actual number of recruited patients with 48 hours LOS were less than the minimum size.

(5) Presentation and preciseness of the results

It is most preferable that the results be reported as relative risk with 95% confidence interval for both quasi-experimental study and cohort study, as it is a more precise method of presentation. However, only two studies (Swoboda et al., 2004; Brandt et al., 2008) presented results in this way. One study (Bracco et al., 2007) reported the outcome as relative risk with p-value. Half of the studies (Barrera et al., 2011; Larson et al., 1985; Ben-Abraham et al., 2002; McManus et al., 1994; Jiang et al., 2003) reported the results in terms of attributive risk (difference of HAI rate between intervention and comparison group) with P-value. Modol et al. (2007) only presented attributive risk without p-value, while

Stout et al. (1998) only reported change of average cases of HAI per year, and these two studies were of the lowest quality regarding to result presentation.

(6) Generalisability of the study results

Two of the ten included studies discussed the issue of generalisability of the research findings, both indicated that generalising these findings might lead to different result or need further discussion (Swoboda et al., 2004; Brandt et al. (2008). Actually, unlike interventions such as drugs and other medical treatment directly used for patients, implementation of infrastructure in a hospital was influenced by the wider hospital setting and country setting, and generalisability of the results to other hospital types or country settings need to be cautious.

Besides, all the findings and conclusions of the studies fitted with other available evidence, except the study by Brandt et al. (2008), which found no benifit of using laminar airflow ventilation system for preventing surgical site infection in operation rooms, which was contrast to the evidence from the HICPAC guideline suggesting the use of ultraclean air for these rooms. The study fulfilled 7 of the 11 criteria for quality assessment, and is of high quality compared with other included cohort studies, thus the effectiveness of the ventilation needs further high quality evidence to reach a consensus.

4.4 Characteristics of included studies

As mentioned in the Research Methodology part, a table of study characteristics was developed and used to extract the key information from each study. The result of study characteristics of each included study was available in Appendix 13.

4.4.1 Characteristics of studies on handwashing infrastructure

Only two studies on handwashing infrastructure met the selection criteria of this review. One (Barrera et al., 2011) used prospective cohort study design to assess the effect of alcohol-based handrub (ABHR) dispensers, and the other one (Swoboda et al., 2004) studied the effect of computerized voice prompts for failure to perform hand hygiene on room exit by using quasi-experimental study design.

Concerning country of origin, the two studies were conducted in Columbia (Barrera et al., 2011) and the USA (Swoboda et al., 2004) respectively. The types of hospital were both university hospital, while one studied 6 intensive care units (Barrera et al., 2011) and the other was based on one surgical intermediate care unit (Swoboda et al., 2004).

With regard to outcome, Barrera et al. (2011) studied overall HAIs and three specific device-associated HAIs, which were central line-associated bloodstream infections (CLABSI), urinary tract infections (UTI), and ventilator-associated pneumonia (VAP); while Swoboda et al. (2004) only focused on the overall HAIs. The follow-up time were 5 years (Barrera et al., 2011) and 15 months (Swoboda et al., 2004) respectively. The outcome measures of the two studies both included a calculation of attributive risk fraction, while only Swoboda et al. (2004) provided result in terms of OR with 95%CI. Outcome of each study was categorized and outlined in Appendix 13.

4.4.2 Characteristics of studies on patient rooms

Four studies meeting the inclusion criteria of this review investigated infrastructure of patient rooms for preventing HAIs. Two used prospective cohort study design (Bracco et al., 2007; Larson et al., 1985), and the other two used retrospective cohort methodology (Ben-Abraham et al., 2002; McManus et al., 1994). Three of the studies explored the effect of single-bed rooms versus multi-bed rooms in reducing HAIs (Bracco et al., 2007; Ben-Abraham et al., 2002; McManus et al., 1994), while the other one studied the increase of space per patient as the main intervention for HAI prevention (Larson et al., 1985).

Three out of the four studies took place in a high income country, two in the USA (Larson et al., 1985; McManus et al., 1994), and one in Canada (Bracco et al., 2007). The other one was based on low income country as Israel (Ben-Abraham et al., 2002). For types of hospitals, one was based on a burn center (McManus et al., 1994), while the other three were all based on ICUs at university affiliated hospital.

The four studies investigated different HAIs as outcome measure, namely, Bracco et al. (2007) explored nosocomial bloodstream infection including MRSA, PSAE, and Candida spp. acquisition and catheter-related infections; Larson et al. (1985)

studied all HAIs as an overall outcome; Ben-Abraham et al. (2002) investigated main pediatric ICU related HAI which were bacteremia, pneumonia, and catheter related infections; while McManus et al. (1994) explored HAI of gram-negative bacteremia (GNB) only.

For the two prospective cohort studies, the follow-up time were both very long, which were 2.5 years or 30 months (Bracco et al., 2007) and 52 months (Larson et al., 1985), respectively. For the two retrospective cohort studies, Ben-Abraham et al. (2002) used somewhat a short 6 months retrospective data and conducted 6 months prospective study; while McManus et al. (1994) used retrospective data of as long as 20 years, 10 years for intervention and 10 years for comparison, respectively.

As regard to outcome presentation, only Bracco et al. (2007) reported relative risk, all the other three studies reported attributive risk. However, none of them provided 95% confidence interval. Outcome of each study were categorized and outlined in Appendix 13.

4.4.3 Characteristics of studies on copper-silver ionization system

Only two studies on copper-silver ionization system met the selection criteria of this review (Modol et al., 2007; Stout et al., 1998). Both of them used prospective cohort study design to evaluate the effect of copper-silver ionization system. Modol et al. (2007) compared the system with continuous chlorination and heat-and-flush methods; while Stout et al. (1998) compared it with superheat-and-flush method for disinfection of hospital water supply system.

Concerning country of origin, the two studies were conducted in Spain (Modol et al., 2007) and the USA (Stout et al., 1998) respectively. The types of hospital were university hospital (Modol et al., 2007)and acute-care hospital (Stout et al., 1998) respectively, with similar scale (630 beds and 530 beds).

Both of the studies investigated nosocomial Legionella disease as outcome. Modol et al. (2007) reported change in disease incidence between intervention and comparison group, while Stout et al. (1998) only reported change in average disease cases per year. Both studies had sufficient long follow-up time, which

were 7 years for Modol et al. (2007) and 3 years for Stout et al. (1998). Outcome of each study were categorized and outlined in Appendix 13.

4.4.4 Characteristics of studies on ventilation system

Two studies on ventilation system in hospital met the inclusion criteria of this review (Brandt et al., 2008; Jiang et al. 2003). Both of them used retrospective cohort study design. Brandt et al. (2008) assessed the benefit of laminar airflow ventilation system compared with traditional turbulent ventilation system; while Jiang et al. (2003) evaluated the effect of different types of ventilation, mainly different in the ratio of the area of the ventilation windows to the volume of the room, and different in whether there was laminar airflow.

The two studies were conducted in Germany (Brandt et al., 2008) and China respectively (Jiang et al. 2003). Brandt et al. (2008) conducted the study in operating rooms of surgery departments in 55 hospitals; and Jiang et al. (2003) was based on isolation rooms at a second affiliated hospital.

For outcome infections, Brandt et al. (2008) investigated six types of severe surgical site infection (SSI) as outcome, while Jiang et al. (2003) assessed the change of infection rate especially for SARS. The study period for retrospective data was 4 years for Brandt et al. (2008) and a short 2 months for Jiang et al. (2003). For reporting of outcome, Brandt et al. (2008) used adjusted odds ratio with 95% confidence interval, and Jiang et al. (2003) presented the outcome as infection rate in each study group and relevant p-values. Outcome of each study was categorized and outlined in Appendix 13.

4.4.5 Triangulation of study characteristics of all included studies

(1) Country of Origin

The ten included studies took place in both developed and developing countries. Four of the studies were conducted in the USA (Swoboda et al., 2004; Larson et al., 1985; McManus et al., 1994; Stout et al., 1998), while the others were carried out in six different countries, namely, Canada (Bracco et al., 2007), Colombia (Barrera et al., 2011), Germany (Brandt et al., 2008), Spain (Modol et al., 2007), China (Jiang et al., 2003) and Israel (Ben-Abraham et al., 2002).

(2) Hospital setting

A variety of hospital settings were based upon for the studies. For the types of hospital, the majority as seven of the ten studies were conducted at university affiliated hospitals. The other three studies took place at a burn center (McManus et al., 1994), an acute-care hospital (Stout et al., 1998), and a second affiliated hospital (Jiang et al., 2003) respectively.

Three of the ten studies were based on the whole hospital, namely, the two studies investigated copper-silver ionization system (Modol et al., 2007; Stout et al., 1998), and the one study explored isolation rooms in a burn center (McManus et al., 1994). The other seven studies were conducted in certain special units of the hospital. To illustrate, three studies were performed at ICUs, one at general ICU (Barrera et al., 2011), one at neonatal ICU (Larson et al., 1985), and the other one at pediatric ICU (Ben-Abraham et al., 2002). Two studies were conducted at surgical care units (Swoboda et al., 2004; Bracco et al., 2007). And the other two studies investigated ventilation system were conducted at operation rooms (Brandt et al., 2008), and isolation rooms (Jiang et al., 2003) respectively.

(3) Study population

Of the ten studies, only Jiang et al. (2003) used healthcare workers as study population for nosocmial infections, which were healthcare workers who worked for the SARS patients. The other studies used patients as participants, and all legible patients who were admitted to the study setting (either certain units or the whole hospital) were recruited as study population. Sample size which includes both intervention and comparison population had a great variation among the studies, ranged from 193 (Ben-Abraham et al., 2002) to 144580 patients (Modol et al., 2007).

Three out of the ten studies provided clear description about all potentially key characteristics of study population, including age and gender, average LOS, and other relevant facts. The other seven studies failed to describe age/gender or LOS or both. From the reported information on the characteristics of participants, it can be seen that Bracco et al. (2007) had the oldest participants with a median age of 65 at a surgical ICU in Canada and meanwhile the shortest median LOS of 1.1 days (they recruited all patients rather than patients of at least 48 hours LOS for HAIs, which was actually inappropriate as discussed in the quality assessment part earlier); while Ben-Abraham et al. (2002) had the youngest participants of an average age of 5.3 at a pediatric ICU in Israel and at the same time the longest median LOS of 25 days. Besides, although Larson et al. (1985)'s study which was based on a neonatal ICU was expected to have the youngest participants, the age information was not reported by the authors. Gender of

participants was approximately equally distributed between groups in the studies which provided a gender description.

(4) Interventions of the study

For interventions and controls please see the individual part described earlier as they belonged to different infrastructure category and could not be summarized as a whole.

(5) HAIs measured as outcome

The ten studies used different nosocomial infections as outcome, potentially depending on either the infrastructure explored or the hospital/unit setting that the study was based on. For the two studies investigating handwashing facilities (Swoboda et al., 2004; Barrera et al., 2011), both of them used overall HAIs as outcome (while the later also especially focused on device-related HAIs as well). For the two studies which explored copper-silver ionization system (Modol et al., 2007; Stout et al., 1998), nosocomial legionnaire's disease was studied.

Other than influenced by the infrastructure, the other six studies seemed to decide the outcome infection based on the types of hospital units or some other facts. Among the four studies on isolation rooms, Bracco et al. (2007) which conducted study in surgical ICU used nosocomial bloodstream infection as outcome (MRSA, PSAE, Candida spp., and catheter-related infections); Ben-Abraham et al. (2002) performing at pediatric ICU identified the outcome as ICU related HAIs (bacteremia, pneumonia, catheter related infections); McManus et al. (1994) which carried out the investigation in a burn center used GNB; while Larson et al. (1985) which was based on neonatal ICU explored overall HAIs. For the two studies on ventilation systems, Brandt et al. (2008) which undertook the study at operating rooms defined the outcome as severe SSI including six specialised infections; while Jiang et al. (2003) which was based upon isolation rooms used nosocomial SARS as outcome to be measured.

CHAPTER 5: DATA SYNTHESIS

5.1 Synthesis of data for each infrastructure category

Narrative synthesis instead of meta-analysis or other analytical synthesis was used, as the infrastructure and outcome measures were quite different among the studies, and narrative synthesis is the most appropriate way to compare and summarise these study findings. To assist comparability, attributive risk fraction (ARF) was calculated by the author to compare the studies that reported HAI

incidence in the intervention and comparison group. As the infrastructure is expected to have a positive effect for reducing HAI incidence, attributive risk (AR) is defined here as HAI incidence in unexposed group minus incidence in exposed group, and the ARF is calculated as AR divided by the incidence in unexposed group, which shows the fraction of risk (actually is risk of reducing HAI incidence) that is due to the exposure (Bailey et al., 2005). The use of ARF is robust to and not affected by baseline incidence and the unit of reporting (as some reported incidence as cases per patients, while some reported as cases per 1000 patient discharges or patient days).

5.1.1 Synthesis of data for handwashing infrastructure

Of the two studies on handwashing facilities, one evaluated the effectiveness of ABHR dispensers (Barrera et al., 2011), while the other one investigated the benefit of computerized voice device for failure to perform hand hygiene on room exit (Swoboda et al., 2004), thus was not comparable. From the perspective of a narrative synthesis, both handwashing facilities had a positive role in reducing overall HAIs. However, their effects were both not significant, where p=0.757 for Barrera et al. (2011) and 95% CI included 1 for Swoboda et al. (2004). Besides, Barrera et al. (2011) additionally assessed the effectiveness of ABHR dispensers for reducing device-related HAIs (CLABSI, VAP, UTI), and found the infection rate significantly decreased for CLABSI, significantly increased for UTI, and had no significant change for VAP, respectively. In general, the two kinds of handwashing facility had no significant benefit for preventing HAIs.

5.1.2 Synthesis of data for patient rooms

Four included studies explored the effect of patients rooms, three of them (Bracco et al., 2007; Ben-Abraham et al., 2002; McManus et al., 1994) studied the effectiveness of single-bed room versus multi-bed room (bay room or open space ward belongs to the type of multi-bed room), and the other one (Larson et al. 1985) focused the impact of space per patient in patient rooms for reduction of HAIs. For the three studies investigating single-versus multi-bed rooms, they used different HAIs as outcome, which were nosocomial bloodstream infection (MRSA, PSAE, Candida spp. acquisition), PICU-related HAIs (bacteremia, pneumonia, catheter related infections), and infection of GNB, respectively, thus the outcomes were not quite comparable but some common points can still be observed by narrative synthesis. Generally, all the three studies found a significant reduction of HAIs when using single-bed rooms compared with multi-

bed rooms, regardless of the special nosocomial infections they examined. The only exception is the rate of arterial line–related infection which did not show significant change in the article by Ben-Abraham et al. (2002). For the impact of space per patient, Larson et al. (1985) showed no significant reduction of overall HAIs even there was a threefold increase from 30 square feet per infant to 100.

5.1.3 Synthesis of data for copper-silver ionization systems

Of the two studies investigating copper-silver ionization systems, both of them compared the installment of copper-silver ionization systems for hospital's hot water system with traditional chemical and physical disinfection methods, which were chlorination and heat-and-flush methods (Modol et al., 2007) and superheat-and-flush method (Stout et al., 1998) respectively. Both of them used nosocomial Legionnaires disease as outcome as Legionella is commonly found to colonize in water distribution systems (Noskin & Peterson, 2001). The outcomes of the two studies both showed a decrease of nosocomial Legionnaires disease after installment of the copper-silver ionization systems, either it be decrease of incidence (Modol et al., 2007) or decrease of cases per year (Stout et al., 1998). However, they both did not conduct statistical test for detecting significance of results, either it be p-value or RR with 95% CI, thus it remains unsure whether the copper-silver ionization system has a positive role in reducing nosocomial Legionnaires disease.

5.1.4 Synthesis of data for ventilation systems

Two of the ten included studies focused on ventilation systems for bringing down HAIs in hospital. One examined the effectiveness of HEPA-filtered laminar airflow ventilation system compared with HEPA-filtered turbulent ventilation system (Brandt et al., 2008), while the other one investigated the impact of laminar airflow ventilation and ratios (m^2/m^3) of ventilation windows to the volume of the rooms, respectively (Jiang et al., 2003). They both examined the effect of laminar airflow ventilation but achieved different result. While Brandt et al. (2008) found no significant benefit of laminar airflow ventilation for reducing severe surgical site infections, Jiang et al. (2003) observed significant lower nosocomial SARS incidence for room with laminar airflow ventilation than room without it. In addition, Jiang et al. (2003) found a significant association that the bigger the ratio (m^2/m^3) of ventilation windows to the volume of the room, the lower the SARS incidence observed. Generally speaking, from the two studies the effect of laminar airflow ventilation system for HAI reduction remains to be

discussed, while higher ratio (m^2/m^3) of ventilation windows to the volume of the room was proved to be more effective for reducing at least SARS incidence and could be potentially an important way to prevent SARS outbreaks among healthcare workers. However, the threshold of this ratio is still unknown.

5.2 Triangulation of data for healthy infrastructure

Among the ten included studies, different types of hospital infrastructure were explored, with corresponding HAIs examined for an association between infrastructure and HAI rate. The association was presented mainly in terms of relative risk or attributive risk fraction (ARF). In the triangulation synthesis, variables measured in the studies were classified to groups for the similarities and differences. Table 2 below outlines the main results regarding to the relationship between hospital infrastructure and HAI incidence in each study.

In general, four out of the ten studies had a statistically significant result, three of them were about single- versus multi-bed rooms (Bracco et al., 2007; Ben-Abraham et al. 2002; McManus et al. 1994) and the other one was about laminar airflow ventilation and ratio (m^2/m^3) of ventilation windows to the volume of the room (Jiang et al. 2003). The rest six studies either had no significant outcome or had contrary significant outcome within its own study, which was the study by Barrera et al. (2011). From all these results, it can be inferred that:

(1) **Useful hospital infrastructure:** Single-bed rooms (compared with multi-bed rooms) for ICU or burn center, and higher ratio (m^2/m^3) of ventilation windows to the volume of the rooms were proved to have a significant positive effect in reducing nosocomial diseases (Bracco et al., 2007; Ben-Abraham et al. 2002; McManus et al. 1994; Jiang et al. 2003). From three out of these four studies which reported ARF as part of the result, it showed that single-bed rooms reduced the incidence of VAP by 55%, central venous catheter-related bacteremia by 62.5%, and infection of GNB by 61.5%, compared with multi-bed rooms; and higher ratio (m^2/m^3) of ventilation windows to the volume of the room reduced the incidence of nosocomial SARS by 56.1%, which were all very dramatic.

(2) **Useless hospital infrastructure:** ABHR dispensers for handwashing, computerized voice device for failure to perform hand hygiene on room exit, spacious room with more space per patient (compared with crowded room),

and installment of copper-silver ionization system were proved to have no significant impact on HAI reduction in the hospital (Barrera et al., 2011; Swoboda et al., 2004; Larson et al., 1985; Modol et al., 2007; Stout et al. 1998).

(3) **Hospital infrastructure with conflicting results:** There is no agreement on the effect of laminar airflow ventilation system from the included studies. Brandt et al. (2008) reported no significant role of laminar airflow ventilation in decreasing incidence of severe SSI, while Jiang et al. (2003) observed a significant association between laminar airflow ventilation with reduction of SARS incidence. However, they also reflected two different transmission situations which were infection during surgery and transmission of communicable disease, respectively.

Table 2. Outline of main variables measured and outcome of each studies

Study	Hospital setting	Intervention (infrastructure)	Comparison	Outcome HAI	Outcome presentation	Main outcome (NS=not significant; S ↓ =significantly decreased; S ↑ =significantly increased; NA=not available)
Handwashing infrastructure						
Barrera et al. 2011	ICU	ABHR dispensers	Non-installment of dispensers	Overall HAI and device –related HAI (CLABSI, VAP, UTI)	P-value and reduction of HAI rate per year.	**NS:** overall HAI (p=0.757) and VAP (p=0.870) **S ↓** : CLABSI (P<0.001, -12.7% per year) **S ↑** : UTI (P=0.002, +8.0% per year)
Swoboda et al. 2004)	Surgical intermediate care unit	Electronic monitoring and computerized voice prompts for failure to perform hand hygiene on room exit	Electronic monitoring only	Overall HAI	OR with 95% CI, and ARF	**NS**: OR with 95% CI was 0.93[0.65, 1.3] for short-term and 0.68 [0.40, 1.16] for long-term. ARF was 10% for short-term and 40% for long-term.
Patient rooms						
Bracco et al. 2007	Surgical ICU	Six single-bed Rooms	A six-bed and a two-bed bay room	Nosocomial bloodstream infection (MRSA, PSAE, Candida spp. acquisition)	RR with p-value	**S ↓** : RR of MRSA, PSAE and Candida spp. acquisition was 0.65, 0.61 and 0.75 respectively. (All p-value < 0.05).
Larson et al. 1985	Neonatal ICU	Spacious 32-bed unit about 100 square feet per infant	Crowded 18-bed unit about 30 square feet per infant	Overall HAI	ARF with p-value	**NS**: The HAI incidence was 9.6% in the new unit and 11.7% in the old unit (AR=17.9%, p=0.17).
Ben-Abraham et al. 2002	Pediatric ICU	Separate isolation rooms	An open single-space unit	PICU-related HAIs (bacteremia, pneumonia, catheter related infections)	ARF with p-value	**S ↓** : The HAI rate of VAP reduced from 40% to 18% (AR=55%, p<0.01); the HAI rate of central venous catheter-related bacteremia reduced from 24% to 9% (AR=62.5%, P<0.05) **NS**: The HAI rate of arterial line–related infection increased from 2.2% to 4.9%

						(AR=-55.1%, P=NS).
McManus et al. 1994	A burn center	Single-bed isolation rooms (IW)	An open ward (OW)	Nosocomial infection of gram-negative bacteremia (GNB)	ARF with p-value	**S ↓** : The HAI rate of GNB reduced from 31.2% to 12.0% (AR=61.5%, P<0.001).
Copper-silver ionization system						
Modol et al. 2007	Whole hospital	Copper-silver ionization system for the hospital's hot water system	Continuous chlorination and heat-and-flush methods	Nosocomial Legionnaires disease	ARF	**NA**: The rate of nosocomial legionellosis decreased from 2.45 to 0.18 cases per 1000 patient discharges (AR=92.7%).
Stout et al. 1998	Whole hospital	Copper-silver ionization system for the hospital's hot water system	Superheat-and-flush method	Nosocomial Legionnaires disease	Difference in average cases per year	**NA**: The average number of cases of legionnaires' disease per year decreased from 6 cases to2 cases.
Ventilation systems						
Brandt et al. 2008	Operating rooms	HEPA-filtered (vertical) laminar airflow ventilation system	HEPA-filtered turbulent ventilation system	Severe surgical site infection (SSI): hip prosthesis, knee prosthesis, appendectomy, cholecystectomy, colon surgery, and herniorrhaphy.	OR with 95% CI	**NS**: OR [95% CI] was 1.63 [1.06, 2.52] for hip prosthesis, 1.76 [0.80, 3.85] for knee prosthesis, 1.52 [0.91, 2.53] for appendectomy, 1.37 [0.63, 2.97] for cholecystectomy, 0.85 [0.49, 1.49] for colon surgery, and 1.48 [0.67, 3.25] for herniorrhaphy.
Jiang et al. 2003	Isolation rooms for SARS cases	Ratios (m^2/m^3) of ventilation windows to the volume of the rooms: 0 for room B but with a laminar flow; 1:95 for room C; 1:40 for room D.	Ratios (m^2/m^3) of ventilation windows to the volume of the rooms: 0 for room A.	SARS	ARF with p-value	**S ↓** : Laminar flow: The SARS incidence was 73.2% for room A, 32.1% for room B (ARF=56.1%, P<0.001) **S ↓** : Ratios (m^2/m^3) of ventilation windows to the volume of the rooms: 73.2% for room A, 27.5% for room C, and 1.7% for room D (ARF_1=62.4%, ARF_2=93.8%, P<0.001).

Note: see Appendix 1 for abbreviations.

CHAPTER 6: DISCUSSION

6.1 Limitation and potential bias in the review process

Although the review strategy was logically planned, and all titles, abstracts, or full text of the articles were carefully read and filtered, there were several limitations and potential bias in the review process. Firstly, it is unlikely to make exhaustive search by using all general infrastructure terms (such as "infrastructure", "construction", "engineering", "design", "facility", "architecture", and "building" used in the search process). Even though these terms were expected to identify the majority of the potential studies, and an ancestry search for reference lists of relevant articles was checked by hand to identify additional studies, the use of specific infrastructure terms such as "handwashing facility", "single-bed room", or "ventilation" and so on could potentially lead to more studies covered.

Secondly, due to the language criterion for English written articles only, some valuable article written in other language could be missed. Furthermore, as three databases in medicine and public health (Medline, PsycINFO, EMBASE) were used, the potentially relevant studies that were not covered by these databases could have been left out. In addition, only one searcher conducted the data screening and extraction, which was potentially prone to researcher bias of occasional inappropriate performance in the selection and extraction process.

6.2 Discussion

6.2.1 Discussion on findings

This review has systematically identified the types of healthy infrastructure in hospital that were investigated for an objective to prevent HAIs, as well as the effectiveness of each infrastructure in reducing HAIs.

The hospital infrastructure included can be categorised into four types, which were handwashing infrastructure, patient rooms, copper-silver ionization system, and ventilation system. The countries that the were studies based on included both developed and developing countries, and the hospital settings involved both whole hospital and a wide range of units, including different ICUs, surgical care units, operation rooms, and isolation rooms. Except one study

which explored HAIs among healthcare workers (Jiang et al., 2003), the other nine studies all examined HAIs among patients.

The four types of hospital infrastructure contained seven specific infrastructure types. Among them, two were proven to be effective for preventing HAIs (single-bed rooms, and higher ratio of ventilation window areas to the rooms), one had conflicting results from two studies (laminar airflow ventilation system), while four were found not to be useful for HAI prevention (ABHR dispensers for handwashing, computerized voice device for failure to perform hand hygiene on room exit, spacious room with more space per patient, and installment of copper-silver ionization system).

For single-bed rooms, there were three included studies and all presented a significant positive role of this infrastructure for HAIs prevention, thus it was considered that strong evidence supported single-bed rooms over multi-bed rooms for the purpose of preventing HAIs. And as showed in the three studies, the implementation of single-bed rooms could reduce the HAIs rate by 55% to 63% compared with multi-bed rooms. For laminar airflow ventilation system which had two included studies with contrary results, it was considered no consensus evidence was met for the effectiveness of this infrastructure. For the rest five types of hospital infrastructure, with each having only one included study showing no significant association between the infrastructure and HAIs rate, it was considered that current evidence showed no benefit for implementing these types of infrastructure to reduce HAIs, but more evidence is needed to be strongly convinced.

6.2.2 Discussion on implication for hospital infrastructure guidelines

Actually there are many existing guidelines relevant to hospital construction or healthcare buildings worldwide, such as the Guidelines for Design and Construction of Hospital and Health Care Facilities (AIA, 2010), Prevention of Hospital-Acquired Infections-A Practical Guide (WHO, 2002), Guidelines for Environmental Infection Control in Health-Care Facilities (Sehulster & Chinn, 2003), the series of publication of Health Technical Memorandum by the UK Department of Health etc, and the recommendations in the guidelines were widely referred to by hospitals. These guidelines were based on many kinds of evidences, including empirical studies, well-established theories, laboratory results and so on. And these guidelines consider not only HAIs, but broader patient safety issues as well as financial and management concerns.

Here the review findings were compared with the recommendations by the most widely used AIA guidelines. For patient rooms, the AIA recommends that private

rooms become the industry standard of all new construction of acute care hospitals (AIA, 2006), which is coincide the review results of a significant benefit of single rooms for reducing HAI. For ventilation windows, they were required by the guideline for patient rooms due to epidemiological, fire safety, and psychological reasons but the size of windows were not mentioned by the AIA. For other hospital infrastructure, the laminar airflow ventilation, ABHR dispensers and for computerized voice device for handwashing, space per patient for patient rooms, and the copper-silver ionization system were not especially recommended for the construction or renovation of hospitals. Although the AIA guidelines took consideration of broader types of evidence and were from a broader perspective of patient safety, the review results of the healthy hospital infrastructure were generally in accordance with the recommendations in the guideline.

Besides, it is worth mentioning that although the study designs of the included ten articles were of high quality (belonged to Level A and Level B of the NHS ranking of evidence), however, the ten studies were not perfect and had different kinds of deficiencies in study quality as showed in the part of "quality assessment". Furthermore, the ten studies were obviously not enough for making comprehensive guidelines, and there exists a dilemma between scarcity of high-quality empirical studies and need for thorough and scientific guidelines. On one hand, scarcity of high-quality studies is somewhat reasonable according to difficulties to conduct single implementation of infrastructure and to get rid of all confounding factors under a complicated hospital environment. On the other hand, as some evidence is better than no evidence, guidelines have to consider all kinds of evidences at current stage, such as the evidences of Level C and Level D of the NHS ranking of evidence (can be articles with other study design, expert opinions, principles, or merely laboratory-based risk assessment) to facilitate practice. But still, more qualified empirical evidences will be needed to support and promote these guidelines.

6.2.3 Discussion on implication for hospital infrastructure practice

HAIs put heavy medical, public health, and financial burdens to society (WHO, 2002), hospital managers and clinicians should take efforts to prevent and reduce the potential HAIs. When building or renovating a hospital, as architects or engineers are not necessarily aware of infection control issues, thus hospital staff have to intervene and work together with them in the hospital design and construction process, use the available evidences and guidelines to maximize the possibility to prevent infection outbreaks and reduce risks.

As presented in this review, single-bed rooms were strongly supported by current evidence to be effective in HAI prevention when compared with multi-bed rooms for ICU and burn center, thus hospital staff should advocate for single-patient rooms in these acute care units in any new hospital construction, expansion, renovation, or redesign. The ventilation windows were necessary for patient rooms, and from this review higher ratio of ventilation windows to the volume of patient rooms had a significant benefit for preventing HAIs, but the critical value of the ratio was not yet identified, thus for practice there should be as least a window for each patient room but the minimum ventilation window size requirements needed for effective prevention of HAIs remains subject to more evidences. For other types of hospital infrastructure included in this review, no significant benefits were found to support the implementation of these infrastructures for the purpose of reducing HAIs. However, before better evidences are developed and estimated, wider guidelines should also be referred to rather than merely consider high-quality studies for real practice.

It is worth mentioning that there are several other issues to consider when constructing or renovating a hospital. First, due to the potential differences in settings and finances of hospitals among different nations, hospital staff should be cautious when using the review findings. Second, when building or renovating a hospital, despite healthy infrastructure concerns, detrimental infrastructure should be considered and avoided as well. As there is a scarcity of studies on detrimental infrastructure, which is very understandable as hospital architecture is initially designed to be protective, and infrastructures were only known as detrimental when an outbreak or prevalent HAIs occurred. In this matter, hospital administrators could refer to the part of “Relationship between infrastructure and HAIs” where a series of facts regarding harmful infrastructures were illustrated. Third, the design of hospital should take consideration not only for HAI prevention, but together with wider patient safety issues, which were discussed in the AIA guideline and other relevant guidelines. Fourth, for HAI prevention, although hospital infrastructure can play an important role, other non-physical interventions such as education, training, hospital management are equally crucial and should be emphasised as well. Last but not least, adoption of new technologies or changes in healthcare institution is influenced by not only the evidence-based knowledge, but also the wider 'macro' level contextual dynamics such as health policy and health system influences, organisational factors (including financial status of hospital in this case), and individual and professional attitudes (including decision makers’ perceptions of innovation evidence where in this case administrators and clinicians of a hospital may hold diverse perceptions in the uptake of innovations) (Kyratsis et al., 2012). Besides, the installations and buildings should fit the legal frames of countries as well. E.g., in Denmark, the energy consumption of buildings is especially

regulated and should be fulfilled by new buildings and change of use and extensions (Danish Enterprise and Construction Authority, 2010).

6.2.4 Discussion on future research

Despite single-bed rooms for acute care units in hospitals which had strong evidence of its effectiveness for preventing HAIs, other types of hospital infrastructure either had single high-quality study as evidence or had conflicting studies with different results. It is suggested that for laminar airflow ventilation which had contrary findings, more studies on this infrastructure for HAI prevention should be performed to assure its real effects. And for the rest of the types of infrastructure included in this review which had weak evidence (single study) supporting no benefit of these infrastructure, including ABHR dispensers, computerized voice device for handwashing, space per patient in patient rooms, and copper-silver ionization system for hospital water supplying system, it is considered preferable if further studies can be carried out to complement these existing findings in order to form a more robust evidence base for making more scientific guidelines and guiding practice.

Besides, from the screening process of this review, some studies excluded were examining intermediate results rather than the direct HAI incidence, such as microorganism colonization on different materials of carpets or floors in hospital, and health behavior compliance for different handwashing infrastructure. It is suggested that some further research linking these indirect outcomes to HAI incidence can be conducted so as to provide evidences of the effectiveness of these infrastructure for preventing HAIs.

When conducting further research on this topic, several issues identified from the quality assessment part of this review should be noticed, to promote the quality of the study. First, it is more appropriate to only recruit patients with more than 48 hours LOS as participants, as usually infections occurred more than 48 hours after admission are considered nosocomial (WHO, 2002). Second, it is crucial to identify and analyse all confounding factors based on local study setting to reflect the true effect of infrastructure, potential confounders could be both important conditions of patients (severity of illness, comorbid illness, treatment, isolation status, device utilities, use of antimicrobials etc) and importance facts about healthcare workers (nurse-to-patient ratios, personnel work experience, clinical practice etc). Third, for outcome presentation, RR with 95% CI or with p-value is more precise and preferred than only reporting attributive risk without test for statistical significance. Last, it is preferable to report detailed information rather than omit it, such as the characteristics of

participants, details of recruiting process and outcome measurement, to facilitate validity and generalisability of the study results.

CHAPTER 7: CONCLUSION

The review has investigated the healthy infrastructure for preventing HAIs. Ten studies concerning seven specific hospital infrastructure types were identified based on the inclusion criteria. On one side, strong evidence supported that single-bed rooms are effective for HAI reduction compared with multi-bed rooms in acute care units in hospitals; some evidence suggested the higher ratio of area of ventilation windows to volume of patient rooms can significantly bring down HAI incidence. On the other side, some evidence suggested no benefits for preventing HAIs by implementation of ABHR dispensers, computerized voice reminders for handwashing, more spacious patient rooms, or copper-silver ionization for water supplying system in hospitals; and conflicting evidences were found for the effectiveness of laminar airflow ventilation system in patient rooms.

Principally, single-bed rooms for acute care units and at least one ventilation window for each patient room in hospitals are strongly advocated for hospital design, construction and renovation, while other types of hospital infrastructure were not supported by current evidence for a recommendation of use for the purpose of reducing HAIs. Further high-quality research is needed for more robust and comprehensive evidence to facilitate relevant hospital infrastructure guidelines and practice.

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APPENDIX

Appendix 1. List of abbreviations used in the review

ABHR: alcohol-based handrub

AIA: American Institute of Architects

AR: attributive risk

ARF: attributive risk fraction

C. difficile: Clostridium difficile

CASP: Critical Appraisal Skills Programme

CI: confidence interval

CLABSI: central line-associated bloodstream infections

CRD: Centre for Reviews and Dissemination

ECDC: European Centre for Disease Control and Prevention

GNB: gram-negative bacteremia

HAI: healthcare acquired infection

HELICS: Hospital in Europe Link for Infection Control through Surveillance

HEPA filter: High Efficiency Particulate Air filter

ICU: intensive care unit

IOM: Institute of Medicine

LOS: length of stay

MRSA: methicillin resistant Staphylococcus aureus

NAO: National Audit Office

NHS: National Health Service OR: odds ratio

PSAE: Pseudomonas aeruginosa

QALY: Quality-Adjusted Life Year

RCT: randomized controlled trial

RR: relative risk or risk ratio

SARS: severe acute respiratory syndrome

SSI: surgical site infection

UTI: urinary tract infections

VAP: ventilator associated pneumonia

VRE: vancomycin-resistant enterococci

WHO: World Health Organization

Appendix 2. An outline of search strategy

Search terms used in literature search	
Key terms	
Population	Not defined
Intervention or implementation	Infrastructure Construction Engineering Design Facility Architecture Building
Outcome	Health care acquired Infections Nosocomial Infections Cross Infection Hospital Infection Healthcare associated Infections Health care associated infections
Setting	Not defined

Study design	Not defined

Search source	
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present PsycINFO 1967 to March Week 1 2012 EMBASE 1980 to 2012 Week 10
Online engine	Google scholar
Other	Hand searching of bibliography of relevant articles

Appendix 3. Search strategy in Medline, PsycINFO, and EMBASE.

Appendix 3a. Search strategy in Medline

Medline Search History			
	Searches	**Results**	**Search Type**
1	Cross Infection/ or Health care acquired Infections.mp.	41776	Advanced
2	Nosocomial Infections.mp. or Cross Infection/	43196	Advanced
3	Cross Infection/ or Health Care Acquired Infections.mp.	41355	Advanced
4	Cross Infection/ or Healthcare Acquired Infections.mp.	41357	Advanced
5	Sanitary Engineering/ or Infrastructure.mp.	12885	Advanced
6	Construction Materials/ or Hospital Design and Construction/ or Facility Design and Construction/ or Construction.mp.	79996	Advanced

7	Engineering.mp. or Engineering/ or Sanitary Engineering/	96182	Advanced
8	Facility Design and Construction/ or Hospital Design and Construction/ or Interior Design and Furnishings/	18342	Advanced
9	Architecture.mp. or Architecture as Topic/	49523	Advanced
10	Building.mp.	45271	Advanced
11	1 or 2 or 3 or 4	43619	Advanced
12	5 or 6 or 7 or 8 or 9 or 10	269275	Advanced
13	11 and 12	852	Advanced
14	**limit 13 to english language**	**693**	**Advanced**

Appendix 3b. Search strategy in PsycINFO

PsycINFO search history			
	Searches	**Results**	**Search Type**
1	Health care acquired Infections.mp.	14	Advanced
2	Nosocomial Infections.mp.	38	Advanced
3	Cross Infection.mp.	14	Advanced
4	Health Care Acquired Infections.mp.	1	Advanced
5	Healthcare Acquired Infections.mp.	3	Advanced
6	Infrastructure.mp.	3541	Advanced
7	Construction.mp.	48839	Advanced
8	Engineering.mp.	11907	Advanced

9	exp Facilities/ or Facility.mp.	64520	Advanced
10	Architecture.mp. or exp Architecture/	8745	Advanced
11	Building.mp. or exp Facilities/	86998	Advanced
12	1 or 2 or 3 or 4 or 5	69	Advanced
13	6 or 7 or 8 or 9 or 10 or 11	162424	Advanced
14	12 and 13	22	Advanced
15	**limit 14 to english language**	**21**	**Advanced**

Appendix 3c. Search strategy in EMBASE

EMBASE search history			
	Searches	**Results**	**Search Type**
1	cross infection/ or hospital infection/ or Health care acquired Infections.mp.	48802	Advanced
2	Nosocomial Infections.mp. or hospital infection/	31527	Advanced
3	hospital infection/ or cross infection/ or Health Care Acquired Infections.mp.	48285	Advanced
4	cross infection/ or hospital infection/ or Healthcare Acquired Infections.mp.	48298	Advanced
5	Infrastructure.mp.	13497	Advanced
6	Construction.mp. or construction work/	80445	Advanced
7	engineering/ or hospital engineering/	6238	Advanced
8	health care facility.mp. or health care facility/	46660	Advanced

9	hospital design.mp. or hospital design/	8317	Advanced
10	Architecture.mp. or architecture/	55746	Advanced
11	building/ or hospital building/	5399	Advanced
12	1 or 2 or 3 or 4	50690	Advanced
13	5 or 6 or 7 or 8 or 9 or 10 or 11	208160	Advanced
14	12 and 13	1214	Advanced
15	**limit 14 to english language**	**1003**	**Advanced**

Appendix 4. A table of criteria for study selection

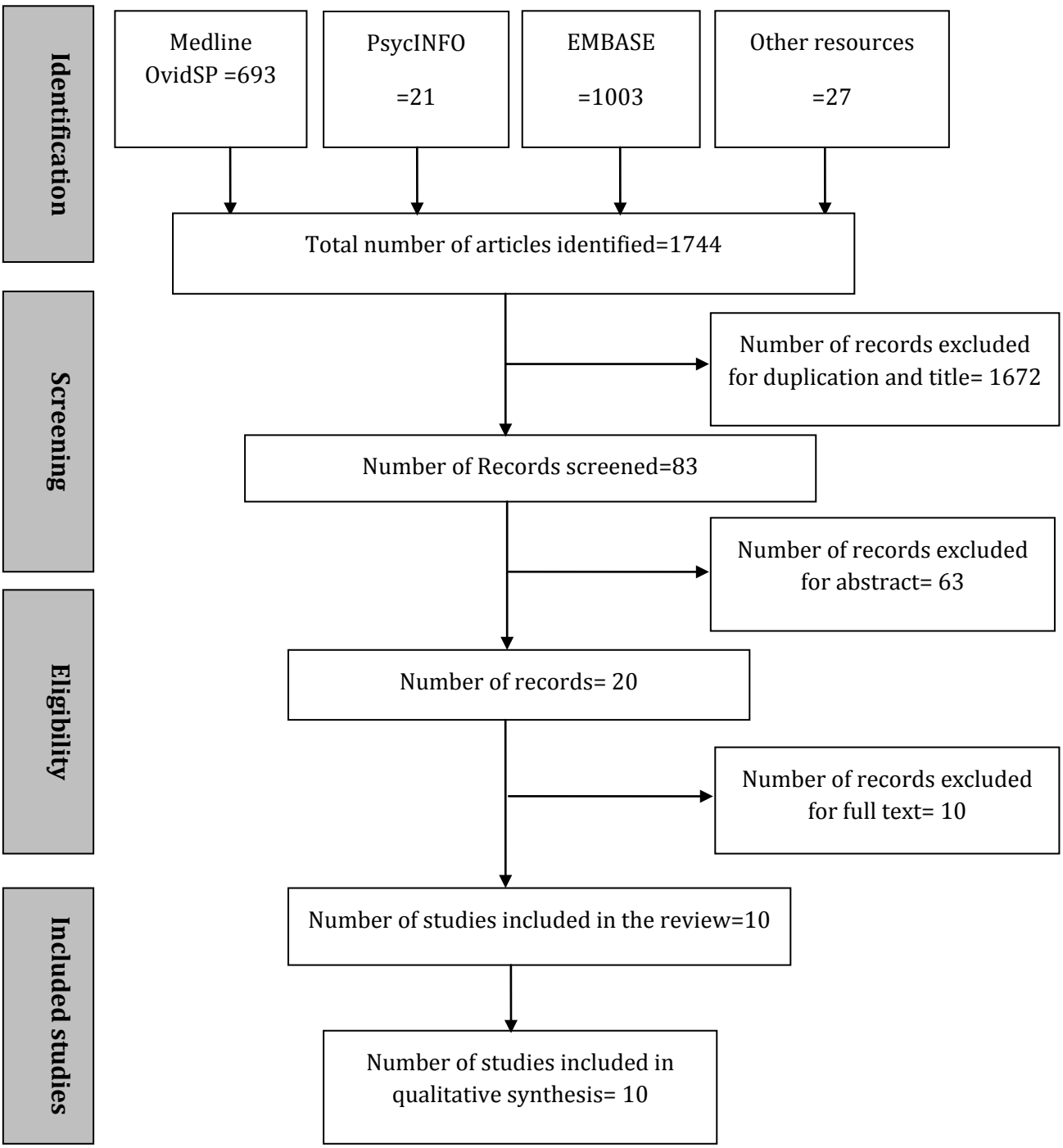
Inclusion and exclusion criteria		
	Inclusion	**Exclusion**
Study design	• Randomised controlled clinical trial (RCT) • Prospective cohort study • Quasi-experimental study	Other forms of study
Intervention	Single infrastructure intervention	Multi-modal interventions
Outcome	Direct outcome as change in infection rates	Indirect outcomes as: • Change in microbe counts • Change in health behaviour compliance
Population and setting	Population in hospital and hospital setting	Other population and settings
Others	• Published in English • Published year later than 1980	• Published in other language • Published year earlier than 1980

Appendix 5. Levels of Evidence used by the UK National Health Service*

Level	Evidence
Level A	Consistent Randomised Controlled Clinical Trial, cohort study, all or none, clinical decision rule validated in different populations
Level B	Consistent Retrospective Cohort, Exploratory Cohort, Ecological Study, Outcomes Research, case-control study; or extrapolations from level A studies.
Level C	Case-series study or extrapolations from level B studies.
Level D	Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles.

*Levels of Evidence (March 2009). Centre for Evidence Based Medicine. Retrieved from www.cebm.net.

Appendix 6. Flow chart of study selection process



Appendix 7. RCT checklist for quality assessment by CASP

10 questions for quality assessment of a randomised controlled trial
1. Did the study ask a clearly-focused question?
2. Was this a randomised controlled trial (RCT) and was it appropriately so?
3. Were participants appropriately allocated to intervention and control groups?
4. Were participants, staff and study personnel 'blind' to participants' study group?
5. Were all of the participants who entered the trial accounted for at its conclusion
6. Were the participants in all groups followed up and data collected in the same way?
7. Did the study have enough participants to minimise the play of chance?
8. How are the results presented and what is the main result?
9. How precise are these results?
10. Were all important outcomes considered so the results can be applied?

Appendix 8. Cohort study checklist for quality assessment by CASP

12 questions for quality assessment of a cohort study
1. Did the study address a clearly focused issue?
2. Did the authors use an appropriate method to answer their question?
3. Was the cohort recruited in an acceptable way?
4. Was the exposure accurately measured to minimize bias?
5. Was the outcome accurately measured to minimize bias?
6A. Have the authors identified all important confounding factors? 6B. Have they taken account of the confounding factors in the design and/or analysis?
7A. Was the follow up of subjects complete enough? 7B. Was the follow up of subjects long enough?
8. What are the results of this study?

9. How precise are the results? And how precise is the estimate of the risk?
10. Do you believe the results?
11. Can the results be applied to the local population?
12. Do the results of this study fit with other available evidence?

Appendix 9. Table of study characteristics for data extraction

1. Study design	1.1 Type of study design
2. Population and setting	2.1 country 2.2 hospital setting 2.3 participants 2.4 sample size 2.5 age and gender 2.6 length of stay in the hospital
3. Intervention and control	3.1 type of hospital infrastructure 3.2 intervention 3.3 comparator
4. Outcome	4.1 type of HAIs measured 4.2 follow-up time 4.3 main findings as change of infection rates 4.4 conclusion

Appendix 10. Included studies for systematic review

	Article	Study design
1	Barrera L, Zingg W, Mendez F, Pittet D (2011). Effectiveness of a hand hygiene promotion strategy using alcohol-based handrub in 6 intensive care units in Colombia. Am J Infect Control. 39: 633–639.	prospective cohort study
2	Swoboda, S. M., Earsing, K., Strauss, K., Lane, S., & Lipsett, P. A. (2004). Electronic monitoring and voice prompts improve hand hygiene and decrease nosocomial infections in an intermediate care unit. Critical Care Medicine, 32(2), 358–363.	quasi-experimental study
3	Bracco D, Dubois M-J, Bouali R, Eggimann P (2007) Single rooms may help to prevent nosocomial bloodstream infection and cross-transmission of methicillin-resistant Staphylococcus aureus in intensive care-units. Intensive Care Med 33:836–840.	prospecive cohort study
4	Larson E, Hargiss CO, Dyk L (1985). Effect of an expanded physical facility on nosocomial infections in a neonatal intensive care unit. Am J Infect Control. 13:16-20.	prospecive cohort study
5	Ben-Abraham, R., Keller, N., Szold, O., Vardi, A., weinberg, m., barzilay, Z., et al. (2002). Do isolation rooms reduce the rate of nosocomial infections in the pediatric intensive care unit? Journal of Critical Care, 17(3), 176–180.	retrospective cohort study
6	McManus, A. T., Mason, A. D., McManus, W. F., & Pruitt, B. A. (1994). A decade of reduced gram-negative infections and mortality associated with improved isolation of burned patients. Archives of Surgery, 129(12), 1306–1309.	retrospective cohort study
7	Modol, J., Sabria, M., Reynaga, E., Pedro-Botet, M. L., Sopena, N., Tudela, P., et al. (2007). Hospital-acquired Legionnaires disease in a university hospital: Impact of the copper-silver ionization system. Clinical Infectious Diseases, 44(2), 263–265.	prospective cohort study
8	Stout JE, Lin YS, Goetz AM, Muder RR. Controlling Legionella in hospital water systems: experience with the superheat-and-flush method and copper-silver ionization. Infect Control Hosp Epidemiol 1998; 19: 911–4.	prospective cohort study
9	Brandt C, Hott U, Sohr D, et al (2008). Operating room ventilation with laminar airflow shows no protective effect on the surgical site infection rate in orthopedic and abdominal surgery. Ann Surg;248:695–700.	retrospective cohort study

10	Jiang, S. P., Huang, L. W., Chen, X. L., Wang, J. F., Wu, W., Yin, S. M., et al. (2003). Ventilation of wards and nosocomial outbreak of severe acute respiratory syndrome among healthcare workers. Chinese Medical Journal, 116(9), 1293–1297.	retrospective cohort study

Appendix 11. Excluded studies and reason for exclusion

	Excluded studies	**Reason for exclusion**
1	Menzies, D., Fanning, A., Yuan, L. And FitzGerald, J.M. (2000) Hospital ventilation and risk for tuberculous infection in Canadian health care workers, Ann. Int. Med., 133, 779–789.	cross-sectional study
2	Tang, J. W., Li, Y., Eames, I., Chan, P. K. S., & Ridgway, G. L. (2006). Factors involved in the aerosol transmission of infection and control of ventilation in healthcare premises. Journal of Hospital Infection, 64(2), 100–114.	general descriptive study
3	Bouza, E., Pelaez, T., Perez-Molina, J., Marin, M., Alcala, L., Padilla, B., et al. (2002).Demolition of a hospital building by controlled explosion: The impact on filamentous fungal load in internal and external air. Journal of Hospital Infection, 52(4), 234–242.	laboratory study for microorganisms only
4	Calder, R.A., Duclos, P., Wilder, M.H., Pryor, V.L. and Scheel, W.J. (1991) Mycobacterium tuberculosis transmission in a health clinic, Bull. Int. Union Tuberc. Lung Dis., 66, 103–106.	Abstract only
5	Creedon, S. A. (2005). Healthcare workers' hand decontamination practices: Compliance with recommended guidelines. Journal of Advanced Nursing, 51(3), 208–216.	multi- intervention
6	Lam, B. C. C., Lee, J., & Lau, Y. L. (2004). Hand hygiene practices in a neonatal intensive care unit: A multimodal intervention and impact on nosocomial infection. Pediatrics, 114(5), E565–E571.	multi- intervention
7	Randle, J., Clarke, M., & Storr, J. (2006). Hand hygiene compliance in healthcare workers. Journal of Hospital Infection, 64(3), 205–209.	multi- intervention

8	Preston GA, Larson EL, Stamm WE. The effect of private isolation rooms on patient care practices, colonization and infection in an intensive care unit. Am J Med 1981;70:641–5.	multi-intervention
9	Kaplan LM, McGuckin M. Increasing handwashing compliance with more accessible sinks. Infect Control 1986;7:408–10	cross sectional study
10	Freeman, J. Prevention of nosocomial infections by location of sinks for hand washing adjacent to the bedside [Abstract 60]. In: Program and abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, 1993:130.	only abstract without full text found
11	Pittet D, Hugonnet S, Harbarth S, Mourouga P, Sauvan V, Touveneau S. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Lancet 2000;356:1307–12.	the major intervention is posters
12	Pittet D. Compliance with hand disinfection and its impact on hospitalacquired infections. J Hosp Infect 2001;48(suppl A):S40–S46.	only rubs, not dispensers
13	Muto, C. A., Sistrom, M. G., & Farr, B. M. (2000). Hand hygiene rates unaffected by installation of dispensers of a rapidly acting hand antiseptic. American Journal of Infection Control, 28(3), 273–276.	multi-intervention
14	Gordin, F. M., Schultz, M. E., Huber, R. A., & Gill, J. A. (2005). Reduction in nosocomial transmission of drug-resistant bacteria after introduction of an alcohol-based handrub. Infection Control and Hospital Epidemiology, 26(7), 650–653.	laboratory study for nosocomial isolates (including both colonization and infection)
15	Lankford, M. G., Zembower, T. R., Trick, W. E., Hacek, D. M., Noskin, G. A., & Peterson, L. R. (2000). Impact of hospital design on the hand washing compliance among healthcare workers. Clinical Infectious Diseases, 31(1), 215–215.	multi-intervention
16	Bigazzi E, Turrisi L, Zagli G, Pecile P, Bonizzoli M, Peris A (2010). Bay rooms vs singlebed rooms in intensive care unit nosocomial infections: a case-control study. Crit Care. 14 (Suppl 1):P458	laboratory study for microorganisms only
17	Larson, E. L., Bryan, J. L., Adler, L. M., & Blane, C. (1997). A multifaceted approach to changing hand washing behavior. American Journal of Infection Control, 25(1), 3–10.	multi-intervention

18	Lankford, M. G., Collins, S., Youngberg, L., Rooney, D. M., Warren, J. R., & Noskin, G. A. (2006). Assessment of materials commonly utilized in health care: Implications for bacterial survival and transmission. American Journal of Infection Control, 34(5), 258–263.	laboratory study for microorganisms only
19	Anderson, R. L., Mackel, D. C., Stoler, B. S., & Mallison, G. F. (1982). Carpeting in hospitals—An epidemiological evaluation. Journal of Clinical Microbiology, 15(3), 408–415.	laboratory study for microorganisms only
20	Harris, D. (2000). Environmental quality and healing environments: A study of flooring materials in a healthcare telemetry unit. Doctoral dissertation, Texas A&M University, College Station.	laboratory study for microorganisms only
21	Noskin, G. A., Bednarz, P., Suriano, T., Reiner, S., & Peterson, L. R. (2000). Persistent contamination of fabric-covered furniture by vancomycin-resistant enterococci: Implications for upholstery selection in hospitals. American Journal of Infection Control,28(4), 311–313.	laboratory study for microorganisms only
22	Noyce, J. O., Michels, H., & Keevil, C. W. (2006). Potential use of copper surfaces to reduce survival of epidemic methicillin-resistant Staphylococcus aureus in the healthcare environment.Journal of Hospital Infection, 63(3), 289–297.	laboratory study for microorganisms only
23	Liu Z, Stout JE, Tedesco L, et al. Controlled evaluation of copper-silver ionization in eradicating Legionella pneumophila from a hospital water distribution system. J Infect Dis 1994; 169:919–22.	laboratory study for microorganisms only
24	Hunfeld KP, Schmidt C, Krackhardt B, et al. Risk of Pseudomonas aeruginosa cross-colonisation in patients with cystic fibrosis within a holiday camp: a molecular-epidemiological study. Wien Klin Wochenschr 2000; 112:329-333. 80. Jones AM, Govan	molecular epidemiological study
25	Kibbler CC, Quick A, O'Neill AM (1998). The effect of increased bed numbers on MRSA transmission in acute medical wards. J Hosp Infect. 39:213-219.	Laboratory study for pathogen colonization only, not infection
26	Halaby T, De Wit R, Al Naiemi N (2011). Impact of a single-room design on the spread of multidrug-resistant bacteria in an intensive care unit. Clinical Microbiology and Infection. Conference: 21st ECCMID/27th ICC Milan Italy.	laboratory study for microorganisms only

27	Goldmann, D. A., Durbin, W. A., & Freeman, J. (1981). Nosocomial infections in a neonatal intensive-care unit. Journal of Infectious Diseases, 144(5), 449–459.	multi-intervention
28	Bonizzoli M, Bigazzi E, Peduto C, Tucci V, Zagli G, Pecile P, Peris A (2011). Microbiological survey following the conversion from a bay-room to single-room intensive care unit design. J Hosp Infect. Jan;77(1):84-6.	laboratory study for microorganisms only
29	Gastmeier, P., Schwab, F., Geffers, C., & Ruden, H. (2004). To isolate or not to isolate? Analysis of data from the German nosocomial infection surveillance system regarding the placement of patients with methicillin-resistant Staphylococcus aureus in private rooms in intensive care units. Infection Control and Hospital Epidemiology, 25(2), 109–113.	cross-sectional study
30	MacKenzie, F. M., Bruce, J., Struelens, M. J., Goossens, H., Mollison, J., & Gould, I. M. (2007). Antimicrobial drug use and infection control practices associated with the prevalence of methicillin- resistant Staphylococcus aureus in European hospitals. Clinical Microbiology and Infection, 13(3), 269–276.	cross-sectional study
31	Wigglesworth, N., & Wilcox, M. H. (2006). Prospective evaluation of hospital isolation room capacity. Journal of Hospital Infection, 63(2), 156–161.	Not about isolation rooms but about isolation failures
32	Jernigan, J. A., Titus, M. G., Groschel, D. H. M., GetchellWhite, S. I., & Farr, B. M. (1996). Effectiveness of contact isolation during a hospital outbreak of methicillin-resistant Staphylococcus aureus. American Journal of Epidemiology, 143(5), 496–504.	Not single room, but room with an anteroom and two beds.
35	Borg, M. A. (2003). Bed occupancy and overcrowding as determinant factors in the incidence of mRsA infections within general ward settings. Journal of Hospital Infection, 54, 316–318.	focus more and bed occupacy
36	Huebner J, Frank U, Kappstein I, et al. Influence of architectural design on nosocomial infections in intensive care units: a prospective 2-year analysis. Intensive Care Med 1989;153:179-183.	multi-intervention
37	Mullin B, Rouget C, Clement C, et al. Association of a private isolation room with ventilator-associated Acinetobacter baumannii pneumonia in a surgical intensive-care unit. Infect Control Hosp Epidemiol 1997;18:499-503	multi-intervention

38	Smith G, Smylie HG, McLauchlan J, Logie JR. Ward design and wound infection due to Staphylococcus pyogenes. J R Coll Surg Edinb 1980;25:76-79.	multi-intervention
39	Vincent J, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe: results of the European Prevalence of Infection in Intensive Care (EPIC) study. JAMA 1995;274:639-644.	1-day point-prevalence study
40	Van Griethusen A, Spies-van Rooijen N, Hoogenboom-Verdegaal A. Surveillance of wound infections and a new theatre: unexpected lack of improvement. J Hosp Infect 1996;34:99-106.	multi-intervention
41	Chattopadhyay B. Control of infection wards: are they worthwhile? J Hosp Infect 2001;47:88-90. 25. McKendrick GD, Edmond	multi-intervention
42	Maki DG, Alvarado CJ, Hassemer CA, Zilz MA. Relation of the inanimate hospital environment to endemic nosocomial infection. N Engl J Med 1982;507:1562-1566.	no full text found
43	Yavuz, s. s., bicer, y., yapici, N., Kalaca, s., Aydin, o. o., Camur, G., et al. (2006). Analysis of risk factors for sternal surgical site infection: Emphasizing the appropriate ventilation of operating theaters. Infection Control and Hospital Epidemiology, 27(9), 958–963.	mutli-intervention
44	Hubad B, Lapanje A (2011). Inadequate hospital ventilation system increases the risk of nosocomial Mycobacterium tuberculosis. Journal of Hospital Infection, Volume 80, Issue 1, P.88-91.	laboratory study for microorganisms only
45	Luke D. Knibbs, Lidia Morawska, Scott C. Bell, Piotr Grzybowski (2011). Room ventilation and the risk of airborne infection transmission in 3 health care settings within a large teaching hospital. American Journal of Infection Control, Volume 39, Issue 10, P. 866-872.	only estimation of infection risks without actual infection rates
46	Yam R, Yuen PL, Yung R, Choi P (2011). Rethinking hospital general ward ventilation design using computational fluid dynamics. Journal of Hospital infection. 77: 31-36.	laboratory study for microorganisms only
47	Jiamjarasrangsi W, Bualert S, Chongthaleong A, Chaindamporn S, Udomsantisuk N, Euasamarnjit W (2009). Inadequate ventilation for nosocomial tuberculosis prevention in public	cross-sectional study

	hospitals in Central Thailand. Int J Tuberc Lung. 13:454-459.	
48	Chen YS , Lin YE, Liu YC, Huang WK, Shih HY, et al (2008). Efficacy of point-of-entry copper--silver ionisation system in eradicating Legionella pneumophila in a tropical tertiary care hospital: implications for hospitals contaminated with Legionella in both hot and cold water. The Journal of hospital infection. Vol. 68, Issue: 2, P 152-158.	laboratory study for microorganisms only
49	Huang HI, Shih HY, Lee CM, Yang TC, Lay JJ, Lin YE (2008). In vitro efficacy of copper and silver ions in eradicating Pseudomonas aeruginosa, Stenophomonas maltophilia and Acinetobacter baumannii: implications for on-site disinfection for hospital infection control. Water Res. 42:73e80.	laboratory study for microorganisms only
50	Pedro-Botet ML, Sanchez I, Sabria M, Sopena N, Mateu L, et al (2007). Impact of copper and silver ionization of fungal colonization of the water supply in health care centers: implications for immunocompromised patients. Clinical Infectious Diseases 45: 84–8	laboratory study for microorganisms only
51	Blanc, D. S., P. Carrara, G. Zanetti, and P. Francioli (2005). Water disinfection with ozone, copper and silver ions, and temperature increase to control Legionella: seven years of experience in a university teaching hospital. J. Hosp. Infect. 60:69-72.	laboratory study for microorganisms only
52	Kusnetsov, J., E. Iivanainen, N. Elomaa, O. Zacheus, and P. J. Martikainen (2001). Copper and silver ions more effective against legionellae than against mycobacteria in a hospital warm water system. Water Res. 35:4217-4225.	laboratory study for microorganisms only
53	Rohr U, Senger M, Selenka F, Turley R, Wilhelm M (1999). Four years of experience with silver-copper ionization for control of Legionella in a German university hospital hot water plumbing system. Clin Infect Dis. 29(6):1507-1511.	laboratory study for microorganisms only
54	Harris, D. D., Pacheco, A., & Lindner, A. S. (2010). Detecting Potential Pathogens on Hospital Surfaces: An Assessment of Carpet Tile Flooring in the Hospital Patient Environment. Indoor and Built Environment, 19(2), 239-249.	laboratory study for microorganisms only
55	Skoutelis AT, Westenfelder GO, Beckerdite M, Phair JP (1994). Hospital carpeting and epidemiology of Clostridium difficile. Am J Infect Control. 22:212-7.	laboratory study for microorganisms only

56	mcManus, A. t., mcManus, w. f., mason, A. D., Aitcheson, A. R., & Pruitt, B. A. (1985). Microbial colonization in a new intensive-care burn unit—A prospective cohort study. Archives of Surgery, 120(2), 217–223.	Laboratory study for pathogen colonization only, not infection
57	Mulin, B., Rouget, C., Clement, C., Bailly, P., Julliot, M. C., Viel, J. F. et al. (1997). Association of private isolation rooms with ventilator- associated Acinetobacter baumanii pneumonia in a surgical intensive-care unit. Infection Control and Hospital Epidemiology, 18(7), 499–503.	laboratory study for microorganisms only
58	Shirani, K. Z., McManus, A. T., Vaughan, G. M., McManus, W. F., Pruitt, B. A., & Mason, A. D. (1986). Effects of environment on infection in burn patients. Archives of Surgery, 121(1), 31–36.	multi-intervention
59	Giannitsioti E, Athanasia S, Antoniadou A, Fytrou H, Athanassiou K, Bourvani P, et al (2009). Does a bed rail system of alcohol-based handrub antiseptic improve compliance of health care workers with hand hygiene? Results from a pilot study. American Journal Of Infection Control.37(2):160-3.	cohort study (for handwashing compliance)
60	Domanico, R., Davis, D., Coleman, F., and Davis, B., Jr. (2010). Documenting the NICU Design Dilemma: Parent and Staff Perceptions of Open Ward versus Single Family Rooms. Journal of Perinatology, Vol. 30, No. 5, pp 343-351.	not about nosocomial infecion, but perspectives only
61	Kaplan LM, McGuckin M. Increasing handwashing compliance with more accessible sinks. Infect Control 1986;7:408–10	cohort study (for handwashing compliance)
62	Bischoff WE, Reynolds TM, Sessler CN, Edmond MB, Wenzel RP. Handwashing compliance by health care workers. The impact of introducing an accessible, alcohol-based hand antiseptic. Arch Intern Med 2000;160:1017–21.	cohort study (for handwashing compliance)
63	Larson E, McGeer A, Quraishi ZA, et al. Effect of an automated sink on handwashing practices and attitudes in high-risk units. Infect Control Hosp Epidemiol 1991;12:422–8.	quasi-experimental study (for handwashing compliance)
64	Wurtz R, Moye G, Jovanovic B. Handwashing machines, handwashing compliance, and potential for cross-contamination. Am J Infect Control 1994;22:228–30.	cohort study (for handwashing compliance)
65	Whitby, M., & McLaws, M. L. (2004). Hand washing in healthcare workers: Accessibility of sink location does not improve	cohort study (for handwashing compliance)

	compliance. Journal of Hospital Infection, 58(4), 247–253.	
66	Vernon, M. O., Trick, W. E., Welbel, S. F., Peterson, B. J., & Weinstein, R. A. (2003). Adherence with hand hygiene: Does number of sinks matter? Infection Control and Hospital Epidemiology, 24(3), 224–225.	cohort study (for handwashing compliance)
67	Larson, E. L., Albrecht, S., & O'Keefe, M. (2005). Hand hygiene behavior in a pediatric emergency department and a pediatric intensive care unit: Comparison of use of 2 dispenser systems. American Journal of Critical Care, 14(4), 304–310.	quasi-experimental study (for handwashing compliance)
68	Ouren D, Tismer S (2010). Evaluation of a new flexible mounting dispenser to improve point of care product access in an acute care hospital and the resulting effect on hand hygiene compliance rates. American Journal of Infection Control. Vol. 38, Issue 5, Page e61.	cohort study (for handwashing compliance)
69	Thomas BW, Berg-Copas GM, Vasquez DG, Jackson BL, Wetta-Hall R (2009). Conspicuous vs customary location of hand hygiene agent dispensers on alcohol-based hand hygiene product usage in an intensive care unit. J Am Osteopath Assoc. 109(5):263-267.	cohort study (for handwashing compliance)
70	Haas JP, Larson EL (2008). Impact of wearable alcohol gel dispensers on hand hygiene in an emergency department. Acad Emerg Med. 15: pp. 393–396.	quasi-experimental study (for handwashing compliance)
71	Birnbach DJ, Nevo I, Scheinman S, Fitzpatrick M, Shekhter I, Lombard JL (2010). Patient safety begins with proper planning: a quantitative method to improve hospital design. Qual Saf Health Care.19: 462– 46.	RCT (for handwashing compliance)
72	Cheng VC, Tai JW, Chan WM, Lau EH, Chan JF, To KK, Li IW, Ho PL, Yuen KY (2010). Sequential introduction of single room isolation and hand hygiene campaign in the control of methicillin-resistant Staphylococcus aureus in intensive care unit. BMC Infect Dis.10:263.	multi-intervention
73	Gordin, F. M., Schultz, M. E., Huber, R. A., & Gill, J. A. (2005). Reduction in nosocomial transmission of drug-resistant bacteria after introduction of an alcohol-based handrub. Infection Control and Hospital Epidemiology, 26(7), 650–653.	laboratory study about nosocomial isolates only.

Appendix 12. Result of quality assessment of each included study using CASP checklists

12a. Quality assessment of studies on handwashing infrastructure (one quasi-experimental study and one prospective cohort study)

CASP checklist of 12 questions for quality assessment of a cohort study	Barrera et al. 2011	CASP checklist of 10 questions for quality assessment of a randomised controlled trial	Swoboda et al. 2004
1. Did the study address a clearly focused issue?	Yes. The study aimed to study whether introduction of alcohol-based handrub dispensers improve handwashing performance and reduce HAIs in 6 intensive care units in Colombia.	1. Did the study ask a clearly-focused question?	Yes. The study aimed to determine whether electronic monitoring of hand hygiene and voice prompts can improve hand hygiene and decrease HAI rates in a surgical intermediate care unit.
2. Did the authors use an appropriate method to answer their question?	Yes. Prospective cohort study is appropriate to answer this research question.	2. Was this a randomised controlled trial (RCT) and was it appropriately so?	No. It is a quasi-experimental study without randomization.
3. Was the cohort recruited in an acceptable way?	No. The cohort recruited every patient admitted to the ICUs. However, it would be more appropriate to only recruit patients who stayed more than 48 hours after admission to be considered nosocomial.	3. Were participants appropriately allocated to intervention and control groups?	No. It is a quasi-experimental study without allocation concealment.
4. Was the exposure	Yes. The infrastructure exposure is objective and	4. Were	Yes. It is impossible and unnecessary to

accurately measured to minimize bias?	there is no classification bias.	participants, staff and study personnel 'blind' to participants' study group?	blind the healthcare personnel to the intervention (voice prompts), however, the review committee (two physicians and one nurse detecting infections were all blinded to phase of the study.
5. Was the outcome accurately measured to minimize bias?	Can't tell. It was not mentioned in detail how they measured the HAIs.	5. Were all of the participants who entered the trial accounted for at its conclusion?	Yes. The performance data of all healthcare personnel were analysed. And HAIs were considered on all patient admissions with a length of stay more than 48 hrs.
6A. Have the authors identified all important confounding factors? 6B. Have they taken account of the confounding factors in the design and/or analysis?	6A. No. Based on their local setting, they identified confounding factors as device utilization, nurse-to-patient ratio, and work experience, but they failed to consider recent antibiotics use as a potential confounder. 6B. Yes. They used Multivariate risk factors analysis model to analyse the confounding factors.	6. Were the participants in all groups followed up and data collected in the same way?	Yes. All data for handwashing performance were collected by electronic monitoring system, and all data for infection rates were collected in the same way by the review committee.
7A. Was the follow up of subjects complete enough? 7B. Was the follow up of subjects long	7A. Can't tell. The follow-up rate was not reported. 7B. Yes. The 5-year follow-up time seems long enough to observe the effect.	7. Did the study have enough participants to minimise the play of chance?	No. Although the power calculation for sample size was conducted, indicating a minimum size of 771 patients per arm. However, the number of patients with a length of stay more than 48 hrs for the three phrases is 204, 194, and 61

enough?			respectively and less than the minimum size.
8. What are the results of this study?	They observed no significant over trend for all HAI (p=0.757) and VAP (p=0.870). There was a significant reduction of CLABSI over time (-12.7% per year; P<0.001), but UTIs increased (+8.0% per year; P=0.002).	8. How are the results presented and what is the main result?	The results were presented in terms of Attributive risk fracture and OR (odds ratio) of infection rate between the intervention (phrase II as short term and Phrase III as long term) and the compactor (phrase I). After adjusting for patient days, (1) the number of infections decreased by 10% in phase II and 40% in phase III; (2) the OR with 95% confidence interval (95%CI) was 0.93[0.65, 1.3] and 0.65, 1.3) and 0.68 [0.40, 1.16] respectively, which means there was no significant difference between the intervention and the comparator.
9. How precise are the results? And how precise is the estimate of the risk?	No. Not every precise, as only attributive risk fraction was reported. Relative risk with confidence interval was not reported.	9. How precise are these results?	Yes. The results were precise as the 95% CI is reported with the OR.
10. Do you believe the results?	Can't tell. The attributive risk fraction of 12.7% per year was obvious and the trend was somewhat steady during the 5 years, but some confounding factors were not considered by the authors as mentioned before.	10. Were all important outcomes considered so the results can be applied?	Yes. All the important features of the hospital settings and the working conditions of the computerized voice prompts were described in detail.

11. Can the results be applied to the local population?	Can't tell. The hospital setting was ICUs in an upper-middle income country. For other types of units or other countries, the use of the study results should be cautious.		
12. Do the results of this study fit with other available evidence?	Yes. Their main study finding was a positive effect of ABHR dispensers, such as those found by others (Pessoa-Silva et al., 2007). And their observation of low nurse-to-patient ratio being independently associated with CLABSI confirmed data from Hugonnet et al (2007) and others describing staff as a key determinant of HAI in critically ill patients.		

12b. Quality assessment of studies on patient rooms (two prospective cohort studies and two retrospective cohort studies)

CASP checklist of 12 questions for quality assessment of a cohort study	**Bracco et al. 2007**	**Larson et al. 1985**	**Ben-Abraham et al. 2002**	**McManus et al. 1994**
1. Did the study address a clearly focused issue?	Yes. The study aimed to assess the effectiveness of singe rooms in preventing nosocomial bloodstream infection in an ICU.	Yes. The study aimed to assess the effect of a threefold increase in space per infant on rates of HAIs in a neonatal intensive care unit.	Yes. The study aimed to deterrmine the effect of isolation rooms on the direct spread of HAIs owing to cross-colonization in a pediatric intensive care	Yes. The study aimed to evaluate and effect of a single-bed isolation (IW) environment compared with an open ward (OW) for the incidence of gram-negative bacteremia

			unit (PICU).	(GNB) in patients with large burns.
2. Did the authors use an appropriate method to answer their question?	Yes. Prospective cohort study is appropriate to answer this research question.	Yes. Prospective cohort study is appropriate to answer this research question.	Yes. Retrospective cohort study is appropriate to answer this research question.	Yes. Retrospective cohort study is appropriate to answer this research question.
3. Was the cohort recruited in an acceptable way?	Yes. The study recruited every patient and considered infections after 48 hours of admission as nosocomial.	Can't tell. The study did not mention in detail the recruitment process.	Yes. The study recruited patients admitted to the PICU for at least 48 hours for HAI detection.	Can't tell. The study did not mention in detail the recruitment process.
4. Was the exposure accurately measured to minimize bias?	Yes. The infrastructure exposure is objective and there is no classification bias.	Yes. The infrastructure exposure is objective and there is no classification bias.	Yes. The infrastructure exposure is objective and there is no classification bias.	Yes. The infrastructure exposure is objective and there is no classification bias.
5. Was the outcome accurately measured to minimize bias?	Yes. Systematic screening was performed consistently for nsococomial disease detection during the study period.	Yes. The infections were screened consistently by the same nurse epidemiologist in the hospital.	Yes. HAIs were monitored using the same definition and criteria.	Yes. They used the same case definition of bacteriema.
6A. Have the authors identified all important confounding factors? 6B. Have they taken	6A. Yes. Based on the local setting, the authors identified confounding factors as emergency admission, mechanical ventilation,	6A. Yes. The study identified mean length of stay, survival rates, mean birth weights, average occupancy rates, nurse-to-	6A. Yes. The studies considered medical and nursing staff, antibiotic administration, protocols, and	6A. No. The study considered burn percentage of body surface, but failed to consider nurse-to-patient

account of the confounding factors in the design and/or analysis?	medical/surgical patient. 6B. Yes. They considered confounding factors in the design (negative pressure was excluded, nurse workforce was matched), and they used multivariate analysis to explore the effect of confounding factors by nominal logistic regression.	patient ratio, clinical practice or patient management, and other parameters to be potential confounding factors. 6B. Yes. In the study design, they assessed that the confounding factors in the old and new units were similar.	procedure of regulations as potential confounding factors. 6B. Yes. They took account of the confounding factors in the analysis, by comparing these factors in the intervention and comparison group (which demonstrated to be similar).	ratio, use of antibiotics, clinical practice and other potential important confounding factors. 6B. Yes. They balanced the burn percentage of body surface for the intervention and comparison group In the study design.
7A. Was the follow up of subjects complete enough? 7B. Was the follow up of subjects long enough?	7A. Can't tell. The study did not report loss to follow-up rate. 7B. Yes. 2.5 years follow-up time seemed long enough.	7A. Can't tell. The study did not report loss to follow-up rate. 7B. Yes. 39 months for comparison and 13 months for intervention seemed long enough.	7A. Can't tell. The study did not report loss to follow-up rate. 7B. Can't tell. 6 months for both intervention and comparison group seemed not long enough compared to other studies.	7A. Can't tell. The study did not report loss to follow-up rate. 7B. Yes. 10 years for both comparison and intervention group seemed long enough.
8. What are the results of this study?	The main result was reported as RR with P-value. By multivariate analysis, the relative risk of MRSA,	The main result was reported as attributive risk (2.1%) with P-value. The nosocomial rate was 9.6%	The result of the study was reported as attributive risk with p-value. HAI rates	The result of the study was reported as attributive risk with p-value. The incidence of

	pseudomonas aeruginosa and Candida spp. acquisition in single rooms or cubicles versus bay rooms was 0.65, 0.61 and 0.75 respectively. (All p-value < 0.05).	in the new unit and 11.7% in the old unit (p=0.17).	(intervention vs comparison group) were 18% vs 40% for VAP (P<0.01); 9% vs 24% for central venous catheter-related bacteremia (P<0.05); and 4.9% vs 2.2% for arterial line–related infection (P=NS).	GNB was 12.0% in the IW (intervention) cohort, and 31.2% in the OW (comparison) cohort (P<0.001).
9. How precise are the results? And how precise is the estimate of the risk?	No. The result was not very precise as 95%CI was not reported with RR.	No. The result was not very precise and relative risk and 95% CI was not reported.	No. The result was not very precise and relative risk and 95% CI was not reported.	No. The result was not very precise and relative risk and 95% CI was not reported.
10. Do you believe the results?	Yes. The p-values indicated there were significant differences, and the potential confounding factors were considered and removed.	Yes. The p-value was reported and the potential confounding factors were considered in the study design.	Can't tell. Although P-value was reported and potential confounding factors were considered. However, the study period of 6 months and the sample size of around 100 patients seemed not quite enough.	Yes. The effect size is big and P-value is quite small (<0.01). Although some potential confounding factors were not reported, but the 20-year study period is long enough to offset some of the defects.
11. Can the results be applied to the local	Can't tell. The hospital setting was where MRSA was not	Can't tell. The hospital setting was neonatal	Can't tell. The hospital setting was pediatric	Can't tell. The hospital setting was 2. A burn

population?	hyperendemic and based on high income country. For other hospital conditions and countries, the use of the study results should be cautious.	intensive care unit (NICU) in a high income country. For other hospital settings and countries, the use of the study results should be cautious.	intensive care unit (PICU) in a low income country. For other hospital settings and countries, the use of the study results should be cautious.	center in a high income country. For other hospital settings and countries, the use of the study results should be cautious.
12. Do the results of this study fit with other available evidence?	Yes. The study result was in line with European and other authorities' recommendation of single rooms in the design of intensive care units (Connell & Humphreys, 2000).	Yes. The study result of no significant association between space per patient and HAI rate, fitted with aother study by Maki et al (1982) concluding that the inanimate environment had little effect on HAI rates.	Yes. The study result of possible effect of isolation rooms in reducing Nis fitted other studies with similar conclusion (Jernigan et al., 1996; Mulin et al., 1997).	Yes. The study result of positive effect of isolation rooms in reducing Nis fitted with other relevant studies (McManus et al., 1985)

12c. Quality assessment of studies on copper-silver ionization system (two prospective cohort studies)

CASP checklist of 12 questions for quality assessment of a cohort study	**Modol et al. 2007**	**Stout et al. 1998**
1. Did the study address a clearly focused issue?	Yes. The study aimed to assess the impact of copper-silver ionization system in the prevention of new cases of Hospital acquired Legionella disease (HALD).	Yes. The study aimed to evaluate of effect of copper-silver ionization system on nosocomial Legionnaires' disease.
2. Did the authors use an appropriate	Yes. Prospective cohort study is appropriate to	Yes. Prospective cohort study is appropriate to

method to answer their question?	answer this research question.	answer this research question.
3. Was the cohort recruited in an acceptable way?	Can't tell. I was not mentioned in detail the recruitment process.	Can't tell. I was not mentioned in detail the recruitment process. However, it is good for the study to consider pneumonia patients who developed symptoms more than 48 hours after admission as nosocomial.
4. Was the exposure accurately measured to minimize bias?	Yes. The infrastructure exposure is objective and there is no classification bias.	Yes. The infrastructure exposure is objective and there is no classification bias.
5. Was the outcome accurately measured to minimize bias?	Can't tell. It was not reported in detail the process of outcome measurement.	Can't tell. It was not reported in detail the process of outcome measurement.
6A. Have the authors identified all important confounding factors? 6B. Have they taken account of the confounding factors in the design and/or analysis?	6A. No. The study failed to consider any confounding factors. 6B. No. The study didn't consider confounding factors in the study design or analysis.	6A. No. The study failed to consider any confounding factors. 6B. No. The study didn't consider confounding factors in the study design or analysis.
7A. Was the follow up of subjects complete enough? 7B. Was the follow up of subjects long enough?	7A. Can't tell. The study didn't provide information about loss to follow-up. 7B. Yes. More than 1.5 years for control group and 5 years for intervention group seemed long enough.	7A. Can't tell. The study didn't provide information about loss to follow-up. 7B. Yes. 13 years for control group and 3 years for intervention group seemed long enough.
8. What are the results of this study?	The resulted was reported in terms of attributive risk (2.27 cases per 1000 patient	The result was reported as decreased average cases per year for legionnaires' disease. The

	discharge). Incidence of nosocomial legionellosis decreased from 2.45 to 0.18 cases per 1000 patient discharges.	average number of cases of legionnaires' disease per year decreased from six cases to two cases.
9. How precise are the results? And how precise is the estimate of the risk?	No. The result was not very precise, as relative risk and 95% confidence interval were not reported.	No. The result was not very precise, as neither proportion nor relative risk with 95% confidence interval were reported.
10. Do you believe the results?	Can't tell. The decrease in Legionella incidence is dramatic, but the study failed to consider confounding factors and didn't report detailed information about recruitment and outcome measure.	Can't tell. The decrease in average legionnaire cases per year is dramatic, but the denominator was not reported. And the study failed to consider confounding factors and didn't report detailed information about recruitment and outcome measure.
11. Can the results be applied to the local population?	Can't tell. The hospital setting was in a hospital where hyperendemic nosocomial legionellosis was present and based on upper-middle income country. For other hospital conditions and countries, the use of the study results should be cautious.	Can't tell. The hospital was an acute-care hospital in a high income country. For other hospital settings and countries, the use of the study results should be cautious.
12. Do the results of this study fit with other available evidence?	Yes. The study found copper-silver system is effective in reducing Legionella colonization of hospital distribution systems, which fits with other studies by Liu et al. (1994) and Stout et al. (1998).	Yes. The study demonstrated the efficiency of copper-silver ionization system in controlling Legionella in an acute-care hospital, which fitted with other studies in vitro and in a non-acute-care hospital setting (Liu et al., 1994; Lin et al., 1996)

12d. Quality assessment of studies on ventilation infrastructure (two prospective cohort studies)

CASP checklist of 12 questions for quality assessment of a cohort study	**Brandt et al. 2008**	**CASP checklist of 11 questions for quality assessment of a case control study**	**Jiang et al. 2003**
1. Did the study address a clearly focused issue?	Yes. The study aimed to evaluate the impact of operating room (OR) ventilation with (vertical) laminar airflow on surgical site infection (SSI) rates.	1. Did the study address a clearly focused issue?	Yes. The study aimed to identify the effect of ventilation of wards in preventing outbreaks of severe acute respiratory syndrome (SARS) among protected healthcare workers in isolation rooms.
2. Did the authors use an appropriate method to answer their question?	Yes. Retrospective cohort study is appropriate to answer this research question.	2. Did the authors use an appropriate method to answer their question?	Yes. Retrospective cohort study is appropriate to answer this research question.
3. Was the cohort recruited in an acceptable way?	Can't tell. They did not mention in detail the recruitment process.	3. Was the cohort recruited in an acceptable way?	Yes. They recruited healthcare workers who worked for the SARS patients as participants.
4. Was the exposure accurately measured to minimize bias?	Yes. The infrastructure exposure is objective and there is no classification bias.	4. Was the exposure accurately measured to minimize bias?	Yes. The infrastructure exposure is objective and there is no classification bias.
5. Was the outcome accurately measured	Yes. The participant hospitals conducted active SSI surveillance according to the methods and	5. Was the outcome accurately measured	Can't tell. They did not mention in detail

to minimize bias?	definitions given by the US National Nosocomial Infection Surveillance system.	to minimize bias?	the outcome measure process.
6A. Have the authors identified all important confounding factors? 6B. Have they taken account of the confounding factors in the design and/or analysis?	6A. Yes. The authors identified potential confounders as wound contamination class, ASA score, operation duration, patients' age and gender, endoscopic operation; number of beds in the hospital, its academic status, operation frequency, and long-term participation in study. 6B. Yes. They performed multivariate analysis for the confounding factors.	6A. Have the authors identified all important confounding factors? 6B. Have they taken account of the confounding factors in the design and/or analysis?	6A. No. The study did not consider any potential confounding factors, such as age, gender, or work experience of the healthcare workers. 6B. No. The study did not consider confounding factors in the study design or analysis.
7A. Was the follow up of subjects complete enough? 7B. Was the follow up of subjects long enough?	7A. Can't tell. The study did not report loss to follow-up rate. 7B. Yes. 4 years of retrospective data seemed long enough.	7A. Was the follow up of subjects complete enough? 7B. Was the follow up of subjects long enough?	7A. Can't tell. The study did not report loss to follow-up rate. 7B. Yes. Two months retrospective data seemed not long, but as they were exploring SARS outbreaks which was irregular and only happened during that period, it is considered as acceptable.
8. What are the results of this study?	8. The result was presented in terms of odds ratio with 95% CI. 3. The adjusted odds ratio [95% CI] of severe SSI for using laminar airflow OR ventilation compared with turbulent ventilation was 1.63 [1.06, 2.52] for hip prosthesis, 1.76 [0.80, 3.85] for knee	8. What are the results of this study?	8. The result was reported as infection rate for each group (where attributive risk can be calculated) and relevant p-values. The SARS infection rate of healthcare workers were 73.2% for room A (ventilation ratio 0), 32.1% for room B

	prosthesis, 1.52 [0.91, 2.53] for appendectomy, 1.37 [0.63, 2.97] for cholecystectomy, 0.85 [0.49, 1.49] for colon surgery, and 1.48 [0.67, 3.25] for herniorrhaphy.		(ventilation ratio 0 and with laminar flow), 27.5% for room C (ventilation ratio 1:95), and 1.7% from room D (ventilation ratio 1:40). The difference in the infection rate was of statistical significance (P<0.001).
9. How precise are the results? And how precise is the estimate of the risk?	9. Yes. The result was precise and 95% CI was reported with the odds ratio.	9. How precise are the results? And how precise is the estimate of the risk?	No. The result was not very precise and relative risk and 95% CI was not reported.
10. Do you believe the results?	10. Yes. The study period is long enough, and all potential confounding factors were adjusted, and outcomes were appropriately measured.	10. Do you believe the results?	10. Can' tell. The study did not take into account the potential confounding factors in the study design or analysis as mentioned before.
11. Can the results be applied to the local population?	11. Can't tell. The hospital setting was operation rooms in a high income country. For other hospital setting and countries, the use of the study results should be cautious.	11. Can the results be applied to the local population?	11. Can't tell. The hospital setting was isolation rooms in a middle income country. For other hospital setting and countries, the use of the study results should be cautious.
12. Do the results of this study fit with other available evidence?	No. The result of no benefit of ventilation is contrast to the evidence from the HICPAC guideline which recommended the use of ultraclean air for the prevention of SSI in ORs (Mangram et al., 1999). And as the authors mentioned, there was no further evidence from	12. Do the results of this study fit with other available evidence?	Yes. The study result of positive role of ventilation for preventing HAIs was somewhat in accordance with the systematic review of the association between ventilation in built environment

	controlled trials supporting the need for clean air conditions since then.		and infectious diseases (Li., 2007).

Appendix 13. Result of study characteristics of each included study

Study	Study design	Population: 1. Country 2. Hospital type 3. Participants 4. Sample size 5. Age and gender 6. Average length of stay	Intervention	Control	Outcome: 1. HAI measured 2. Study duration (Follow-up time) 3. Main findings 4. Main conclusion
Handwashing infrastructure					
Barrera et al. 2011	prospective cohort study	1. Colombia 2. 6 intensive care units (ICU) in the University Hospital of Valle, Cali, Colombia: general (internal medicine and cardiovascular surgery), 10 beds; trauma, 8 beds; neurosurgery, 4 beds; burn,	Alcohol-based handrub (ABHR) dispensers were installed between February and	Before the ABHR dispensers were installed.	1. All HAI, and will focus on device-associated HAIs, which are central line-associated bloodstream infections (CLABSI), ventilator-associated pneumonia (VAP), and urinary tract infections (UTI). 2. 5 years (from January 2001 to December 2005).

		15 beds; pediatric (PICU), 7 beds; and neonatology (NICU), 40 beds. 3. (1) For the intervention, all healthcare personnel in the ICUs participated; (2) For the outcome, all patients entered ICUs were monitored for HAI. 4. 14,516 patients cumulating 166,498 patient-days. 5. Median age 36 [21-55]; nearly equal gender. 6. Median (IQR): 5 days [2-12]	June 2002 (Each ICU bed/place was equipped with a dispenser).		3. They observed no significant over trend for all HAI (p=0.757) and VAP (p=0.870). There was a significant reduction of CLABSI over time (-12.7% per year; P<0.001), but UTIs increased (+8.0% per year; P=0.002). Multivariate risk factor analysis suggested a low nurse-to-patient ratio to be independently associated with CLABSI incidence rates. 4. Use of ABHR dispensers has the potential to reduce CLABSI rates rapidly.
Swoboda et al. 2004	quasi-experimental study (Three-phase)	1. USA 2. A surgical intermediate care unit (IMC) in a university, tertiary-care institution (Johns Hopkins Hospital). It has 9 rooms, 14 beds. 3. (1) For the intervention: All healthcare personnel. (2) For the outcome: All patients with a length of stay >48 hrs were followed for HAI. Patients were pre- and postoperative surgical patient. 4. 1,875 patients were admitted to the IMC for 3,549 patient days (459 patients with a length of stay	Electronic monitoring and computerized voice prompts for failure to perform hand hygiene on room exit (phase II for short-term effect and Phrase III for long-term	Electronic monitoring only (Phase I).	1. overall rate of HAIs 2. 15 months (from July 2000 to October 2001). 3. After adjusting for patient days, they found (1) the number of infections decreased by 10% in phase II and 40% in phase III (attributable risk fraction); (2)the odds ratio (OR) of HAI rates with 95% confidence interval (95%CI) was 0.93[0.65, 1.3] for Phrase II compared with Phrase I; and 0.68 [0.40, 1.16] for Phrase III compared with Phrase I; (3) There was a decrease in HAI rate after intervention, but the association between HAI and individual phase was not significant. 4. Computerized voice prompts had both a short-term and, perhaps, a longer-term

		more than 48 hrs were considered for HAI calculation for the 3 phrases). 5. Median age 62 [16-99]; nearly equal gender. 6. Median (range): 8 days [2–61].	effect).		effect in decreasing nosocomial diseases.
Patient rooms					
Bracco et al. 2007	prospective cohort study	1. Canada 2. A 14-bed medico-surgical ICU at a tertiary teaching hospital affiliated to the University of Montreal. 3. All patients admitted from 1 July 2002 to 31 December 2004 (Infections occurring later than 48 h after admission or within 48 h of discharge were considered as ICU acquired Infection) 4. 2522 patients 5. Average age 65 for both intervention and comparison group; 61% and 67% of men in intervention and comparison group. 6. Median (interquartile) length of stay was 1.1 (1.0–3.0) days	Six single-bed Rooms (8.7 to 9.2m^2 per bed)	A six-bed and a two-bed bay room (between 7.1 and 7.2 m^2)	1. Nosocomial bloodstream infection, of MRSA, of PSAE, and of Candida spp. acquisition. 2. 2.5 years (30 months) 3. By multivariate analysis, the relative risk of MRSA, PSAE, and Candida spp. acquisition in single rooms or cubicles versus bay rooms was 0.65, 0.61 and 0.75 respectively. (All p-value < 0.05). 4. In an institution where MRSA is not hyperendemic, infection control measures may be more effective to prevent cross-transmission of microorganisms in patients housed in single rooms.

Larson et al. 1985	prospective cohort study	1. USA 2. A neonatal intensive care unit (NICU) at University Hospital, Seattle. 3. critically ill infants 4. 1443 patient discharges when the old unit was studied, and 502 when the new unit was studied. 5. Not reported. 6. Mean length of stay was 21 days for survivors and 9 days for nonsurvivors in the old unit. In the new unit, it was 21 and 6 days.	Spacious 32-bed unit about 100 square feet per infant (threefold increase in space per infant, and two isolation rooms were available; 39 months from January 1977 to March 1980)	Crowded 18-bed unit about 30 square feet per infant (There were six small cubicles that housed as many as 4 babies; 13 months from April 1980 to April 1981)	1. All HAIs 2. 52 months 3. (1) The HAI rate was 9.6% in the new unit and 11.7% in the old unit (p=0.17). There was no significant difference in the two units. (2) There was a marked decrease in the numbers of clusters of HAI occurring in the new unit. 4. There was no significant decrease of HAI in new unit compared with the old unit. However, cross-infections between infants were probably minimized in the new unit.
Ben-Abraham et al. 2002	Retrospective cohort study	1. Israel 2. A pediatric intensive care unit of 6-bad at a university-affiliated tertiary referral hostpial. 3. Critically ill pediatric patients. 4. 78 for comparison group and 115 for intervention group. 5. Gender was not reported. Average age was 5.3±1.3 in	Separate isolation rooms (prospectively from May to October 1995)	An open single-space unit (retrospectively from May to October 1992)	1. Main PICU-related HAIs: bacteremia, pneumonia, catheter related infections. 2. 6 months retrospective data and 6 months follow-up time. 3. Nosocomial infection rates (intervention vs comparison group) were 18% vs 40% for VAP (P<0.01); 9% vs 24% for central venous catheter-related bacteremia (P<0.05); and 4.9% vs 2.2% for arterial line–related infection (P=NS). 4. There was possible beneficial effect of single isolation rooms in reducing HAI in

		comparison and 5.7±0.9 in intervention group. 6. 25±6 for comparison group and 11±6 days for intervention group			the PICU.
McManus et al. 1994	Retrospective cohort study	1. USA 2. A burn center 3. Patients with large burns (≥20%) 4. 1605 patient admissions for comparison and 914 for intervention group. 5. Gender was not reported. Mean age was 31.3 for comparison and 32.2 for intervention group 6. LOS was not reported.	Single-bed isolation rooms (IW) (prospectively 1984 to 1993).	An open ward (OW) (retrospectively 1974 to 1983).	1. Nosocomial infection of gram-negative bacteremia (GNB) 2. 10 years for both intervention and comparison group 3. The incidence of GNB was 12.0% in the IW (intervention) cohort, and 31.2% in the OW (comparison) cohort (P<0.001). 4. Improvement in isolation of burned patients were associated with decreased incidence of GNB.
Copper-silver ionization system					
Modol et al. 2007	prospective cohort study	1. Spain 2. A university hospital of 630 beds. 3. All patients with hospital acquired pneumonia 4. 33469 patient discharges for control group and 111111 (calculated from the article) patient discharges for intervention group. 5. Not reported 6. Not reported	Installment of a copper-silver ionization system for the hospital's hot water system (from October 1999 to December	Continuous chlorination and heat-and-flush methods (from January 1998 to September 1999).	1. Hospital-acquired Legionnaires disease (HALD) 2. 7 years (from January 1998 to December 2004). 3. Incidence of nosocomial legionellosis decreased dramatically, from 2.45 to 0.18 cases per 1000 patient discharges. 4. The study demonstrated the efficacy of the copper-silver ionization system in stopping a dramatic situation of endemic HALD.

			2004).		
Stout et al. 1998	prospective cohort study	1. USA 2. An acute-care hospital of 550 beds (The Pittsburgh Veterans' Affairs Health Care System, Oakland Division). 3. All patients who had pneumonia with onset of symptoms more than 48 hours after admission. 4. Not reported 5. Not reported 6. Not reported	Copper-silver ionization system in 3 years (1994 to 1997)	Superheat-and-flush method in previous 13 years (from 1981 to 1994)	1. Nosocomial legionnaire's disease 2. 3 years (36 months) 3. The average number of cases of legionnaires' disease per year decreased from 6 cases to2 cases. 4. A properly maintained and monitored copper-silver ionization system was more effective than the superheat-and-flush method for reducing the nosocomial legionnaires' disease.
Ventilation system					
Brandt et al. 2008	Retrospective cohort study	1. Germany 2. Operating rooms in 63 surgery departments in 55 hospitals 3. All patients undertook surgery in the operation rooms 4. Sample size was calculated as 99230 operations. 5. Not reported 6. Not reported	HEPA-filtered (vertical) laminar airflow ventilation system	HEPA-filtered turbulent ventilation system	1. Severe surgical site infection (SSI) including hip prosthesis, knee prosthesis, appendectomy, cholecystectomy, colon surgery, and herniorrhaphy. 2. 4 years (from 2000 to 2004) 3. The adjusted odds ratio [95% CI] of severe SSI for using laminar airflow OR ventilation compared with turbulent ventilation was 1.63 [1.06, 2.52] for hip prosthesis, 1.76 [0.80, 3.85] for knee prosthesis, 1.52 [0.91, 2.53] for appendectomy, 1.37 [0.63, 2.97] for cholecystectomy, 0.85 [0.49, 1.49] for colon surgery, and 1.48 [0.67, 3.25] for herniorrhaphy.

					4. Operation room (OR) ventilation with laminar airflow showed no benefit and was even associated with a significantly higher risk for severe SSI after hip prosthesis.
Jiang et al. 2003	Retrospective cohort study	1. China 2. Isolation rooms for SARS cases in a second affiliated hospital 3. Healthcare workers caring for isolating SARS cases in the hospital 4. 431 healthcare workers 5. Not reported. 6. Not reported.	Ratios (m^2/m^3) of the area of the ventilation windows to the volume of the rooms: 0 for room B (no window but with a laminar flow); 1:95 for room C; 1:40 for room D.	Ratios (m^2/m^3) of the area of the ventilation windows to the volume of the rooms: 0 for room A (no window).	1. Severe acute respiratory syndrome (SARS) 2. 2 months (from January 30 to March 30, 2003) 3. The SARS infection rate of healthcare workers were 73.2% for room A, 32.1% for room B, 27.5% for room C, and 1.7% from room D. The difference in the infection rate was of statistical significance ((P<0.001)). 4. Good ventilation for isolation SARS cases might be beneficial for preventing outbreaks of SARS among healthcare workers.

Appendix 14. Student Declaration (for research that does not involve human participation or analysis of secondary data)

School of Health and Related Research
Research Ethics Review
for Postgraduate-Taught Students

Form 1B: Student Declaration (for research that does not involve human participation or analysis of secondary data)

To be included in Appendices of dissertation

→ **Research Project Title:**

Systematic review of the effectiveness of healthy hospital infrastructure to prevent healthcare acquired infections

In signing this Student Declaration I am confirming that:

My proposed project will **not** i**nvolve people participating in research either directly** (e.g. interviews, questionnaires) **and/or indirectly** (e.g. people permitting access to data).

My proposed project does not therefore require an ethics review and I have not submitted a Research Ethics Application Form.

→ **Name of student:**
Qing Fang

→ **Signature of student:** **Date:** 27 April, 2012

→ **Name of supervisor:**

Dr Elsebeth Tvenstrup Jensen

→ **Signature of Supervisor**: **Date:** 7 May, 2012