Water-, Sanitation-, and Hygiene-Based Healthcare-Associated Infections
in the Low- and Middle-Income Countries of South and East Asia:
A Systematic Review

By

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Chapter 1: Introduction

Research Question

What is the prevalence of healthcare-associated infections related to water, sanitation, and hygiene in low- and middle-income countries in South and East Asia? What types of pathogens and types of infections are associated with healthcare-associated infections?

Introduction

As the era of the 2015 Millennium Development Goals draws to a close, focus is on the post-2015 Sustainable Development Goals. These goals are to be met by the year 2030. The new goals will include "universal access to basic water, adequate sanitation and adequate handwashing" in healthcare facilities. The proposed post-2015 Sustainable Development Goals contains 17 goals (Table 1). Within the sixth goal, Goal 6.1. aims to achieve universal and equitable access to safe and affordable drinking water for all.[1]

Table 1: Proposed Post-2015 Sustainable Development Goals [1]

1. End poverty in all its forms everywhere.
2. End hunger, achieve food security and improved nutrition and promote sustainable agriculture.
3. Ensure healthy lives and promote well-being for all at all ages.
4. Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all.
5. Achieve gender equality and empower all women and girls.
6. Ensure availability and sustainable management of water and sanitation for all.
7. Ensure access to affordable, reliable, sustainable and modern energy for all.
8. Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all.
9. Build resilient infrastructure, promote inclusive and sustainable industrialization and foster innovation.
10. Reduce inequality within and among countries.
11. Make cities and human settlements inclusive, safe, resilient and sustainable.
12. Ensure sustainable consumption and production patterns.
13. Take urgent action to combat climate change.
14. Conserve and sustainably use the oceans, seas and marine resources for sustainable development.
15. Protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss.
16. Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels.
17. Strengthen the means of implementation and revitalize the global partnership for sustainable development.

Proposed supporting indicators have been recommended by a working group led by IRC, WaterAid, the Water Supply and Sanitation Collaborative Council, United States Agency for International Development (USAID), Human Rights to Water and Sanitation, and the Water and Sanitation Program. The World Health Organization (WHO)/United Nations Children's Fund (UNICEF) Joint Monitoring Programme (JMP) for Water Supply and Sanitation also facilitated international consultations. The proposed supporting indicator 2 intends to achieve universal access to basic drinking water, sanitation, and hygiene (WASH) for households, schools and health facilities.[2] To gauge whether or not those goals and the supporting indicator are met, proposed measurable indicators were developed. The following proposed measures would evaluate the quality of WASH in health care facilities:

1) percentage of health facilities with an improved source on premises and water points accessible to all users at all times;

2) percentage of health facilities with basic separated sanitation facilities for males and females on or near premises (at least one toilet for every 20 users at inpatient centres, at least four toilets – one each for staff, female, male and child patients – at outpatient centres);

3) percentage of health facilities with a hand washing facility with soap and water in or near sanitation facilities, food preparation areas and patient care areas; and

4) percentage of health facilities with basic separated sanitation facilities for females that provide privacy; soap, water and space for washing hands, private parts and clothes; and places for changing and disposing of materials used for managing menstruation.[2]

Using clean water, appropriate sanitation, and good hygiene is thought to prevent healthcare-associated infections (HAIs).[3] This literature reviews the prevalence of HAIs related to WASH in the low- and middle-income countries of South and East Asia as there are no systematic reviews on HAIs particularly in low- and middle-income countries in this region. There is also a growing concern in Asia about antimicrobial resistance, which can complicate treatment of HAIs and spread across international boundaries.[4] Figure 1 maps the countries included in this review and Table 2 lists the countries. The World Bank defines countries with low- or middle-income economies as having a gross national index per capita of less than $12,746.[5]

Figure 1: Low- and Middle-Income Countries of South and East Asia

Table 2: Low- and Middle-Income Countries of South and East Asia[3]

South Asia	
Afghanistan	Maldives
Bangladesh	Nepal
Bhutan	Pakistan
India	Sri Lanka
East Asia	
American Samoa	Myanmar
Cambodia	Palau
China	Papua New Guinea
Fiji	Philippines
Indonesia	Samoa
Kiribati	Solomon Islands
Democratic People's Republic of Korea	Thailand
Laos	Timor-Leste
Malaysia	Tuvalu
Marshall Islands	Tonga
Micronesia	Vanuatu
Mongolia	Vietnam

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Chapter 2: Literature Review

Healthcare-associated Infections

Healthcare-associated infection (HAI) is a transmitted infection that occurs from a health care facility setting. There are various definitions of HAIs.[1] The Centers for Disease Control and Prevention (CDC) and the National Healthcare Safety Network (NHSN) defines an HAI more generally as a "localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s)," in which there is no evidence of an infection upon admission to the healthcare facility.[2] Colonization or inflammation are not considered infections since colonization does not cause symptoms or clinical signs of infection and inflammation is not always due to a microorganism.[2] A systematic review found the most common definition of healthcare-associated infection in the literature – the patient must have received intravenous therapy or wound care at home within 30 days before the infection, attended a hemodialysis clinic in the previous 30 days, received intravenous chemotherapy in the previous 30 days, stayed in an acute care hospital for at least two days within 90 days before the infection, or recently lived or is living in a long-term care facility or a nursing home.[1]

Each type of infection has its own criteria for diagnoses. The CDC/NHSN developed diagnostic criteria for various types of HAIs – urinary tract infections (UTI); surgical site infections (SSI); bloodstream infections (BSI); pneumonia (PNEU); bone and joint infections (BJ); central nervous system infections (CNS); cardiovascular system infections (CVS); eye, ear, nose, or mouth infections (EENT); gastrointestinal system infections (GI); lower respiratory tract infections other than pneumonia (LRI); reproductive tract infections (REPR); skin and soft tissue infections (SST); and systemic infections (SYS). The criteria help determine if an infection is present and if it is healthcare-associated. Criteria also include clinical signs, clinical symptoms, and laboratory-confirmed results.[2]

Burden of Healthcare-Associated Infections

High-Income Countries

Worldwide, the burden of HAI remains high, increasing morbidity, mortality, length of hospital stay, and costs.[3] In high-income countries, 5 – 15% of hospitalized patients and 9 – 37% of patients in intensive care units acquire at least one HAI (Table 2).[3] In Europe, an estimated 5 million HAIs occur yearly, adding 25 million days of hospitalization and an extra $15 – 28 billion USD spent on health care, according to an infection control surveillance collaboration consisting of data from Austria, Belgium, Germany, Spain, Finland, France, Hungary, Lithuania, the Netherlands, England, Northern Ireland, Scotland, and Wales.[3] In the United States, the estimated incidence of HAIs in 2002 was 9.3 infections per 1000 patient-days, affecting 1.7 million patients with approximately 99,000 deaths due to HAIs (Table 2).[4] Yearly, HAIs cost the U.S. about $6.5 billion USD.[5]

Through the National Nosocomial Infection Surveillance System, the United States collects annual cost data on certain types of HAIs linked to medical devices and procedures (Table 1).[6]

Table 1: Costs of Types of Healthcare-Associated Infections[6]

Type of Infection	Cost per Infection (in U.S. dollars)	Total Annual Cost (in U.S. dollars)
Surgical Site Infection (SSI)	10,443 – 25,546	3.2 billion – 8.6 billion
Central Line-Associated Bloodstream Infection (CLABSI)	5,734 – 22,939	590 million – 2.68 billion
Ventilator-Associated Pneumonia (VAP)	11,894 – 25,072	780 million – 1.5 billion
Catheter-Associated Urinary Tract Infection (CAUTI)	589 – 758	340 million – 370 million
Clostridium difficile-Associated Disease (CDI)	5,042 – 7,179	1.01 billion – 1.62 billion

The burden of various HAIs varies in high-income countries. One study found that the most common types of HAIs in the U.S. were UTI (36%), then SSI (20%), followed by BSI (11%) and PNEU (11%) (Table 2).[4] In the same U.S. study, there was an estimated 98,987 deaths related to HAIs in 2002. Among these deaths, an estimated 35,967 were pneumonia infections, 30,665 were bloodstream infections, 13,088 were urinary tract infections, 8,205 were surgical site infections, and 11,062 were other-site infections (Table 2).[4]

Patients in the intensive care unit (ICU) have higher HAI prevalence than those in other medical wards.[7-8] Patients in the ICU are at higher risk of HAI due to a higher likelihood of certain health statuses, the presence of acute diseases, increased use of treatments that may weaken the immune system or expose the patient to more pathogens, and increased use of invasive procedures.[7] In the U.S., the prevalence of HAI in ICU patients is 9 – 37%,[7] and in Europe, the prevalence of HAI in ICU patients is 19.5% (Table 2).[8] In 2002, the U.S. infection rate of HAIs in the ICU was 13.0 per 1000 patient-days (Table 2).[4] The most common type of HAI in the ICU was found to be respiratory tract infections in the United States[7] and respiratory tract and bloodstream infections in Europe (Table 2).[8] Risk of respiratory tract infection in the ICU increases with endotracheal intubation, mechanical ventilation, and aspiration.[7] In ICUs in the U.S., the highest mortality rate was due to healthcare-associated bloodstream infections at 25% and the lowest was found to be in surgical site infections at 11% (Table 2).[4] In Europe, the ten most common HAI-related pathogens in the ICU include *Escherichia coli* (15.9% of positive microbiological results), *Staphylococcus aureus* (12.3%), *Enterococcus* species (9.6%), *Pseudomonas aeruginosa* (8.9%), *Klebsiella* species (8.7%), coagulase-negative *Staphylococci* (7.5%), *Candida* species (6.1%), *Clostridium difficile* (5.4%), *Enterobacter* species (4.2%), *Proteus* species (3.8%), and *Acinetobacter* species (3.6%).[8]

Pediatric patients generally have a higher risk of HAI than adult patients because of underdeveloped immune systems, naïve immune systems, congenital or acquired immune deficiencies, and increased close physical contact.[9] In a review of literature on HAI in high-income countries, the prevalence of HAIs in pediatric wards ranged from 1.4% to 24.2% and the incidence ranged from 4.6 to 59.7 per 1000 patient-days (Table 2).[9] In pediatric intensive care units, the three most common HAIs were bloodstream infections, followed by pneumonia, and urinary tract infections (Table 2).[9]

Bloodstream infections were associated with the highest mortality - 3% mortality rate in pediatric patients and 11% mortality rate in neonates with very low birthweight (Table 2).[9] Pediatric patients are at higher risk of certain pathogens, including respiratory virus infections, rotavirus, varicella zoster virus, pertussis, and tuberculosis, compared to adults due to immune function and higher likelihood of transmission.[9]

Low- and Middle-Income Countries

As for low- and middle-income countries, a meta-analysis evaluated the burden of HAIs by looking at the prevalence, incidence, and densities of HAI in low- and middle-income countries in Africa, the Americas, the Eastern Mediterranean, Europe, South-East Asia, and the Western Pacific.[10] Prevalence of HAIs varied between 5.7 – 19.% and the incidence of HAIs ranged between 9.0 – 91.7 episodes per 1000 patient-days (Table 2).[10] Another review found the prevalence of HAIs in low- and middle-income countries to be 7.2 – 21.6% in Argentina, China, Thailand, the Philippines, Panama, Colombia, Bangladesh, and Senegal (Table 2).[11] A review of Sub-Saharan African literature, found the prevalence of HAIs in that region to be 6.7 to 28%.[12] In low- and middle-income countries, HAIs increase hospital length of stay from 6 to 23 days in non-ICU medical wards per case.[13]

Reports of overall costs of HAI in low- and middle-income countries are limited and varied. In Brazil, HAIs were estimated to cost $18 million USD in 1992.[13] In Mexican ICUs, the cost of HAI was estimated at $12,155 USD per case and for a catheter-associated bloodstream infection, the cost was estimated to be an additional $11,591 USD per case.[13] In Argentina ICUs, the average cost of catheter-related bloodstream infections was $4,888 USD per case, and the average cost of healthcare-associated pneumonia was $2,255 USD per case.[13] In Turkey, ventilator-associated pneumonia increased the total healthcare cost per patient by four-fold from $2,315 to $6,308 USD per case.[14] In India, healthcare-associated bacteremia added an extra $14,818 USD to the hospital stay, while it added an extra $15,275

USD in the United States, implying that the increase in healthcare cost due to a case of bacteremia may be similar in high-income and low/middle-income countries.[15] Although each cost study may have their own definitions for types of costs and may include different factors to calculate costs, the studies show that HAIs increase health care costs in both high-income and low/middle-income countries.

Surgical-site infections (SSI) were found to be the most common type of HAI in low- and middle-income countries, significantly higher than in high-income countries (Table 2).[10] A review of HAIs in Sub-Saharan Africa also showed SSIs to be the most studied.[12] The incidence of surgical-site infections was 1.2 – 23.6 per 100 surgical procedures with pooled cumulative incidence of surgical-site infections at 5.6 (95% CI: 2.9 – 10.5) per 100 surgical procedures. The study further assessed the incidence of different types of SSIs.[10] Contaminated surgical wounds were defined as fresh accidental wounds with major breaks in sterile technique or large spillage into the gastrointestinal tract.[16] Contaminated wounds had a median cumulative incidence of 14.3 (range 0.5 – 65.5) episodes per 100 surgical procedures.[10] Finally, dirty-infected surgical wounds were defined as perforations in old wounds.[16] Dirty-infected surgical wounds had a median cumulative incidence of 39.2 (range 0.2 – 100.0) episodes per 100 surgical procedures. Overall, the more dirty the surgical wound, the higher the median cumulative incidence.[10]

Patients in the ICU in low- and middle-income countries also have a higher prevalence of HAIs compared to patients in the medical wards. The reported prevalence ranged from 8.8 to 40.5 per 100 patients (Table 2).[11] The pooled cumulative incidence was 47.9 episodes per 1000 patient-days (Table 2).[10] An analysis was done comparing adult ICU HAI incidence rates between high-income and low/middle-income countries.[3] The low- and middle-income countries included in this analysis were Argentina, Brazil, Colombia, India, Mexico, Morocco, Peru, and Turkey while the high-income country included was the United States. The adult ICU catheter-related bloodstream infection incidence rate in the U.S. was 4.0/1000 catheter-days while it was more than three-fold higher in low- and middle-income countries at 12.5/1000 catheter-days. The adult ICU ventilator-associated pneumonia (VAP) incidence rate in the U.S. was 5.4/1000 ventilator-days while it was almost five-fold higher at 24.1/1000 ventilator-days in low- and middle-income countries. The adult ICU catheter-related UTI incidence rate in the U.S. was 3.9/1000 catheter-days while it was more than twice higher at 8.9/1000 catheter-days in low- and middle-income countries.[3]

Epidemiologic studies have been done on HAIs among pediatric patients in low- and middle-income countries. HAI occurred in 0.9 – 17.7% of patients in pediatric wards and 2.7 – 26.9% of patients in children's hospitals (Table 2).[10] In the pediatric ICU areas, the incidence of HAIs was 1.6 – 46.1 episodes per 1000 patient-days. Incidence of pediatric catheter-related bloodstream infections was 10.2 – 60.0 (median 18.7) per 1000 catheter-days. Incidence of pediatric ventilator-associated pneumonia (VAP) was 4.4 to 143 (median 28.0) per 1000 ventilator-days. In neonatal ICU units, the incidence of HAI was 15.2 – 62.0 per 1000 patient-days.[10] Another review noted that bloodstream neonatal healthcare-acquired infections are up to 20 times higher in low- and middle-income countries than in high-income countries, which had bloodstream infection rates of 1-5 per 1000 livebirths reported.[17]

A study compared pediatric ICU HAI incidence rates between high-income and low/middle-income countries.[3] The pediatric ICU catheter-related bloodstream infection incidence rate was 6.6/1000 device-days in the U.S. while it was more than double at 16.1/1000 catheter-days in low- and middle-income countries. The pediatric ICU VAP incidence rate was 2.9/1000 ventilator-days in the U.S., while it was almost four-fold higher at 10.6/1000 device-days in low- and middle-income countries. Finally, the pediatric ICU catheter-related UTI incidence rate in the U.S. was 4.0/1000 device-days while it was 5.4/1000 device-days in low- and middle-income countries.[3]

High-Income Countries Versus Low/Middle-Income Countries

As shown in Table 2, low- and middle-income countries have higher estimated rates of HAIs than high-income countries, in general. The most common types of HAIs vary based on location. The difference of average excess length of hospital stay due to HAIs was difficult to compare between high-income and low/middle-income countries from the literature found. The excess days from HAIs in high-income countries was calculated per annum while the excess days from HAIs in low- and middle-income countries was calculated per case.[3,13] Excess costs due to HAIs is also difficult to compare between high-income and low/middle-income countries with the limited and varied information from low- and middle-income countries.

Table 2: Estimated Burden of Healthcare-Associated Infections in High Income and Low/Middle-Income Countries[3-4,7-11]

	High Income Countries			Low/Middle-Income Countries		
	Overall	**ICU**	**Pediatrics**	**Overall**	**ICU**	**Pediatrics**
Prevalence (%)	5 – 15 [3]	9 – 37 [3,7]	1.4 – 24.2 [9]	5.7 – 21.6 [10,11]	8.8 – 40.5 [11]	0.9 – 26.9 [10]
Incidence (per 1000 patient-days)	9.3 [4]	13.0[4]	4.6 – 59.7 [9]	9.0 – 91.7 [10]	47.9 [10]	-
Most Common Types of HAI	Urinary Tract[4]	Respiratory Tract,[7-8] Bloodstream[8]	Bloodstream[9]	Surgical-Site[10]	-	-
Type of HAI with Highest Mortality Rate	Pneumonia[4]	Bloodstream[4]	Bloodstream[9]	-	-	-

[10] low- and middle-income countries in Africa, the Americas, the Eastern Mediterranean, Europe, South-East Asia, and the Western Pacific
[11] Argentina, China, Thailand, the Philippines, Panama, Colombia, Bangladesh, and Senegal

High-Income and Low/Middle-Income Countries in Southeast Asia

A new systematic review, published in 2015, of HAI studies in all countries in Southeast Asia, identified 41 studies from six countries.[18] The countries were Indonesia, Malaysia, the Philippines, Singapore, Thailand, and Vietnam. Singapore is considered a high-income country and the others are low- and middle-income countries. The overall mortality attributed to HAIs ranged from 7% to 46%. HAIs increased the hospital length of stay by 5 to 21 days. In Vietnam, cost of hospital stay was $865 USD more for patients with HAI than for patients without HAI. In Thailand, the cost of hospital stay was $1091 USD more for patients with surgical-site infections (SSI) than for those without SSIs. In Singapore, the cost of hospital stay was $4959 USD more for patients with multi-drug resistant bacteremia than for those without the infection. Also in Singapore, the cost of hospital stay was $13,000 USD more for patients with methicillin-resistant *Staphylococcus aureus* than for patients without the infection. The most common pathogens identified by this review included *Pseudomonas aeruginosa, Klebsiella* species, and *Acinetobacter baumannii.*[18]

Healthcare-Associated Infections in Non-Patients

Not only are patients affected by HAIs, but visitors, healthcare personnel, and communities are affected by them, as well, in both high-income and low/middle-income countries. A systematic review was done in 2006 of tuberculosis (TB) in healthcare workers (HCWs) in low- and middle-income countries due to concern about the transmission of *Mycobacterium tuberculosis* from patients to HCWs.[19] Low- and middle-income countries carry more than 90% of the worldwide TB burden. Fifty-one studies in 17 countries were included in the review. The prevalence of latent TB infection in HCWs ranged from 33% to 79%. The annual incidence of TB in HCWs ranged from 69 to 5,780 per 100,000 HCWs. The annual excess attributable risk, compared to the general population, ranged from 25 to 5,361 per 100,000 people. Risk was higher in facilities that had more patients with TB. The highest risk areas included inpatient TB facilities, laboratories, internal medicine wards, and emergency facilities.[19]

Pathogens in Healthcare-Associated Infections

Pathogens in healthcare-associated infections include bacteria, viruses, fungi, and protozoa. The majority of HAIs studied are caused by bacteria.[3,4,7,8,10,12,13,17,18] There are two major classes of bacteria – commensal and saprophytic. Commensal bacteria are normal patient flora that enter sterile body sites, and saprophytic bacteria are found in the environment, such as water, air, and soil.[20]

Bacterial isolates from certain types of HAIs were evaluated in low- and middle-income countries.[10] Among high-risk patients, the most common HAI pathogens are Enterobacteriaceae, excluding *Escherichia coli* (20%, 272 of 1382 isolates), *Acinetobacter* species (19%, 259 of 1382 isolates), and *Pseudomonas* species (17%, 239 of 1382 isolates). High-risk patients are patients in ICUs, patients with burns, and patients admitted for transplants. Among mixed populations, the most common pathogens found are *Staphylococcus aureus* (21%, 266 of 1269 isolates), Enterobacteriaceae, excluding *E.coli* (18%, 231 of 1269 isolates), and *Pseudomonas* species (17%, 214 of 1269 isolates). Mixed populations include all patients in the hospital, including high-risk patients. Among surgical-site infection-related isolates, the most common pathogens found are Enterobacteriaceae, excluding *E.coli* (26%, 284 of 1078 isolates), *Staphylococcus aureus* (20%, 219 of 1078 isolates), and *E. coli* (18%, 193 of 1078 isolates). Among healthcare-associated pneumonia-related isolates, the most common pathogens found are *Pseudomonas* species (29%, 134 of 459 isolates), Enterobacteriaceae, excluding *E.coli* (20%, 92 of 459 isolates), and *Staphylococcus aureus* (10%, 47 of 459 isolates). Among bloodstream infection-related isolates, the most common pathogens found are *Staphylococcus aureus* (19%, 154 of 825 isolates), *Acinetobacter* species (18%, 146 of 825 isolates), and coagulase-negative *Staphylococci* (17%, 141 of 825 isolates) (Table 3).[10]

Surveillance data from the United States from 2009-2010 tracked the most common pathogens found in hospitals (Table 3) and the various types of HAIs.[21] *Staphylococcus aureus* was the most common pathogen overall in the U.S., particularly in surgical-site infections and pneumonia in the U.S. In both high-income and low/middle-income countries, *Staphylococcus aureus* is one of the most common pathogens. Coagulase-negative staphylococci were the most common pathogens in bloodstream infections in the U.S.[21]

Table 3: Most Common Pathogens in Low/Middle-Income Countries and the U.S.[10,21]

Types of Patients or Infections	Low/Middle-Income Countries[10]	United States[21]
High-Risk Patients	Enterobacteriaceae – excluding *E.coli* (20% of pathogens), *Acinetobacter* species (19%), *Pseudomonas* spp. (17%)	-
Mixed Populations	*Staphylococcus aureus* (21%), Enterobacteriaceae – excluding *E.coli* (18%), *Pseudomonas* spp. (17%)	*Staphylococcus aureus* (15.6% of pathogens), *Escherichia coli* (11.5%), coagulase-negative staphylococci (11.7%)
Surgical-Site Infections	Enterobacteriaceae – excluding *E.coli* (26%), *Staphylococcus aureus* (20%), *Escherichia coli* (18%)	*Staphylococcus aureus* (30.4%), coagulase-negative staphylococci (11.7%), *Escherichia coli* (9.4%)
Pneumonia (in high-income countries, ventilator-associated only)	*Pseudomonas* spp. (29%), Enterobacteriaceae – excluding *E.coli* (20%), *Staphylococcus aureus* (10%)	*Staphylococcus aureus* (24.1%), *Pseudomonas aeruginosa* (16.6%), *Klebsiella pneumoniae/oxytoca* (10.1%)
Bloodstream Infections (in high-income countries, catheter-related only)	*Staphylococcus aureus* (19%), *Acinetobacter* species (18%), coagulase-negative staphylococci (17%)	coagulase-negative staphylococci (20.5%), *Staphylococcus aureus* (12.3%), *Enterococcus faecalis* (8.8%)

Antimicrobial Resistance

Increased evidence of antimicrobial resistance in pathogenic microorganisms in HAIs is a growing concern. With quickly spreading drug resistant-bacteria, low- and middle-income countries may not have the finances available for newer drugs developed to treat drug resistant infections.

Asia has a large and growing issue with multi-drug resistant bacteria (Table 4).[22] Methicillin-resistant *Staphylococcus aureus* (MRSA) is common in Singapore.[22] Vancomycin-intermediate *S. aureus* (VISA) and vancomycin-resistant *S. aureus* (VRSA) were found in Japan.[22] VRSA is also in India.[22] Extended-spectrum beta-lactamase (ESBL) *Klebsiella penumoniae* and *Escherichia coli* are found worldwide.[22] Multidrug-resistant *Acinetobacter baumannii* is found in Singapore and Thailand.[22] Carbapenem-resistant Enterobacteriaceae (CRE) is a major issue throughout Asia.[22] They have been found in sewage and tap water in India and Vietnam.[22] Overall prevalence or incidence rates of the resistant pathogens in Asia are unavailable.[22]

The prevalence of antimicrobial resistance in the United States has been studied (Table 4). Surveillance data from 2009-2010 by the Centers for Disease Control and Prevention showed that methicillin-resistant *Staphylococcus aureus* was the most common resistant pathogen - 8.5% of all HAIs during that time period.[21] Vancomycin-resistant enterococci are the second most common at 3% of HAIs. Other resistant pathogens include extended-spectrum cephalosporin-resistant *Klebsiella pneumoniae/oxytoca* (2%), extended-spectrum cephalosporin-resistant *Escherichia coli* (2%), extended-spectrum cephalosporin-resistant *Enterobacter* species (2%), carbapenem-resistant *Pseudomonas aeruginosa* (2%), carbapenem-resistant *Klebsiella pneumonia/oxytoca* (<1%), carbapenem-resistant *Escherichia coli* (<1%), and carbapenem-resistant *Enterobacter* species (<1%) (Table 4).[21] The carbapenem-resistant *Klebsiella, Escherichia,* and *Enterobacter* species are part of a whole group called carbapenem-resistant enterobacteriaceae, which is growing concern in Asia.[22]

Table 4: Antimicrobial Resistant Pathogens in Asia and the United States[21,22]

	Asia[22]	**United States[21]**
Drug-Resistant Pathogens	- Methicillin-resistant *Staphylococcus aureus* - Vancomycin-intermediate *Staphylococcus aureus* - Vancomycin-resistant *Staphylococcus aureus* - Extended-spectrum beta-lactamase *Klebsiella pneumoniae* - Extended-spectrum beta-lactamase *Escherichia coli* - Multidrug-resistant *Acinetobacter baumannii* - Carabapenem-resistant Enterobacteriaceae	- Methicillin-resistant *Staphylococcus aureus* (8.5% of HAIs) - Vancomycin-resistant enterococci (3%) - Extended-spectrum cephalosporin-resistant *Klebsiella pneumoniae/oxytoca* (2%) - Extended-spectrum cephalosporin-resistant *Escherichia coli* (2%) - Extended-spectrum cephalosporin-resistant *Enterobacter* species (2%) - Carbapenem-resistant *Pseudomonas aeruginosa* (2%) - Carbapenem-resistant *Klebsiella pneumoniae/oxytoca* (<1%) - Carbapenem-resistant *Escherichia coli* (<1%) - Carbapenem-resistant *Enterobacter* species (<1%)

[22]The review included studies mostly from Singapore.

A systematic review was done on the presence of antimicrobial resistance with community-associated infections (CAIs) on neonatal patients, comparing data from 1991 – 1995 and from 1996 – 2007 in low- and middle-income countries worldwide.[23] During the first time period, *Staphylococcus aureus* had no resistance to methicillin and chloramphenicol. Only 6% were resistant to gentamicin. Subsequently, during the second time period, 4% of *Staphylococcus aureus* samples were resistant to methicillin, 25% to chloramphenicol, and 17% to gentamicin. During the first time period, 33% of *Klebisella* species was resistant to ampicillin/amoxicillin, gentamicin, and ceftriaxone, compared to the resistance during the second time period – 97% to ampicillin/amoxicillin, 60% to gentamicin, and 66% to ceftriaxone. In the first time period, 40% of *E.coli* was resistant to cotrimoxazole, 8% to ampicillin/amoxicillin, 8% to gentamicin, 20% to chloramphenicol, and no resistance to ceftriaxone or amikacin. In contrast, during the second time period, resistance increased to78% for cotrimoxazole, 72% for ampicillin/amoxicillin, 13% for gentamicin, 44% for chloramphenicol, 19% for ceftriaxone, and 15% for amikacin.[23]

These CAIs can spread to become HAIs. Based on a model looking at transmission of infections between the community and a healthcare facility, an increase in community-associated infection can cause an increase in HAIs that are the same as the community-associated infection. Transmission can occur in waiting rooms of healthcare facilities and in patients' rooms when infective visitors are present.[24] In Asia, there has been documented transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) clones between the community and hospitals.[25]

Water, Sanitation, and Hygiene in Healthcare-Associated Infections

HAIs are caused by either endogenous or exogenous sources. Endogenous sources originate from the patient's body. These microorganisms are normally found in or on the human's body. In an endogenous-based infection, the pathogen either invades another area of the body in which is typically does not reside (e.g. urinary tract infections caused by *E.coli*) or it overgrows other normal flora (e.g.

colitis caused by *C.difficile*) to cause harm to the person. In contrast, exogenous sources come from outside sources, such as healthcare workers, visitors (e.g. skin infections caused by *S.aureus*), other patients (e.g. tuberculosis), equipment (e.g. catheter-associated bloodstream infection caused by coagulase-negative staphylococci), or other aspects of the environment (legionella).[2] Based on the definition, water, sanitation, and hygiene (WASH)-related pathogens come from exogenous sources.

Water in Healthcare-Associated Infections

Water is used in health care facilities for a wide range of purposes, such as drinking, sanitation, ventilation, air conditioning, baths, physiotherapy, birthing pools, and the cleaning of equipment, laundry and units.[26] In a 2014 review of waterborne healthcare-associated infections mainly in Europe and the United States, all the waterborne pathogens were from exogenous sources.[26] Drinking water was the most common source of infection. The point of use was the main source of contamination. The review also cited studies where distilled water was contaminated during storage. Some of the areas where contaminated water was detected include sinks, showers, bathtubs, water taps, automatic devices, drainage systems, water distribution systems, dialysis machines, humidifying incubators, mechanical ventilators, bottled water, water-retaining toys, soaps, an aquarium, and holy water.[26]

Waterborne diseases in healthcare facilities are caused by bacterial, viral, and protozoan pathogens, mainly those excreted in feces.[27] Possible water-based transmission routes include 1) the fecal-oral route, 2) the oral-oral route via saliva, 3) the gastric-oral route via contaminated vomit, and/or 4) gastric-gastric route through contaminated endoscopes. Bacterial enteropathogens include *Salmonella* species, *Shigella* species, *Campylobacter* species, *Escherichia coli*, *Yersinia enterocolitica*, *Vibrio cholerae*. Non-enteric bacterial pathogens that may occur naturally in water and multiply in water include *Pseudomonas aeruginosa, Aeromonas* species, *Legionella* species, nontuberculosis mycobacteria. Pathogenic protozoa include *Giardia, Cryptosporidium, Cyclospora, Isospora,* and microsporidia. Pathogenic viruses include hepatitis A (HAV), hepatitis E (HEV), viral gastroenteritis pathogens (rotavirus, calicivirus, astrovirus, and enteric adenovirus.[27]

Sanitation and Hygiene in Healthcare-Associated Infections

Improper sanitation and hygiene may cause HAIs.[28] Poor sanitation and hygiene may be related to fecal, contact, respiratory, and bloodborne transmission based on the types of pathogens involved. Common enteric HAI organisms include *Clostridium difficile*, hepatitis A, *Klebsiella* species, and norovirus.[29] *Helicobacter pylori* is another infection that appears to be related to poor hygiene. However, the transmission is not fully understood.[27] Some common HAI organisms transmitted via contact (especially through equipment) include certain gram-negative organisms (e.g. enterobacteriaceae), Enterococci species, and *Staphylococcus aureus*. The main respiratory transmitted HAI organisms include influenza and tuberculosis. Common bloodborne HAI pathogens are hepatitis B virus, hepatitis C virus, and human immunodeficiency virus.[29]

One study in 2004 reviewed the global burden of disease due to contaminated injections in health care settings.[30] Unsafe injections can be caused by accidental needlesticks or reuse of needles without sterilization. In 10 world regions with generally high child and adult mortality in 2000, 39.3% of injections were given with reused and unsterilized equipment. These injections led to an estimated 21 million hepatitis B (HBV) infections (32% of new infections), two million hepatitis C (HCV) infections (40% of new infections), and 260,000 human immunodeficiency virus (HIV) infections (5% of new infections). The new infections were calculated to have a burden of 9,177,679 disability-adjusted life years (DALYs) from 2000 to 2030.[30]

Health care waste, although not defined as sanitation by the World Health Organization, is also an important mode of HAI transmission.[28] Sanitation in healthcare facilities is currently only defined in terms of access and quality of toilets.[28] In Bangladesh, a study was done to analyze the country's hospital waste management.[31] At the time of the study, the country only had guidelines for health care facilities on waste management but no established regulations. Hospitals and clinics in Dhaka City were included in the study from June to August 2000 and March 2001. Waste segregation was found to be practiced with sharps only. Infectious wastes, such as used materials and equipment, excrement, and blood were not separated from general waste. Many hospitals also dumped their wastes in public garbage bins, roads, waterways, and other hospital surroundings. The wastes were commonly collected by the general public and re-sold. Seventy-eight percent of the doctors and 69% of the nurses surveyed noted that there were no formal waste treatment systems besides boiling or autoclave. The analysis of the disposed hospital waste showed *Vibrio cholerae*, mycobacteria, amoeba, and *Salmonella* species. The improper waste management of healthcare facilities can cause contamination in soil, groundwater, surface water, and air, potentially affecting the health of the surrounding community. Eleven percent of the nurses and cleaners and 19% of the waste pickers and local residents were found to have infectious diseases 15 days after exposure to health care wastes. The infectious diseases included skin diseases, allergy, hepatitis B, hepatitis C, diarrhea, and dysentery. Sixty-seven percent of cleaners and 68% of waste pickers and local residents encountered physical injury with exposure of medical waste.[31]

Studies Linking WASH and HAI

The importance of WASH to prevent HAIs is generally implied. Not many studies directly study HAIs liked to water, sanitation, or hygiene. One German study conducted in 2001 looked at *Pseudomonas aeruginosa* infections in a surgical intensive care visit due to a point-of-use water filtration.[32] Colonization of *Pseudomonas aeruginosa* in tap water and infection of *Pseudomonas aeruginosa* in patients were evaluated in 2-week intervals for 24 months. Tap water quality before and after the installation of a filter were compared, as well as infection in patients before and after the instillation of the filter. Tap water colonization and Pseudomonal infection were significantly associated. The risk of Pseudomonal infection was significantly reduced in the post-filter cohort.[32]

A 2008 study in Italy studied the molecular epidemiology of *Legionella pneumophila* in a hospital water system.[33] A five-year program monitored the water distribution system in a hospital after installation of a continuous chlorine dioxide treatment in the system and evaluated the treatment method. Molecular typing was used to determine the circulation and persistence of Legionella in the hospital. Although the treatment method did not eradicate *Legionella pneumophila*, the risk management plan may have helped prevent nosocomial legionellosis.[33]

A recent article from China described the impact of removing waterborne pathogens from tap water in a liver transplant unit.[34] The study was conducted between 2009 and 2011. The implementation of point-of-use water filters successfully eradicated *Legionella* species, *Pseudomonas aeruginosa*, *Mycobacterium* species, and filamentous fungi from the water supply in the unit.[34]

A study from Iraq linked nosocomial pediatric diarrhea to sanitation and hygiene.[35] In a cross-sectional study conducted in 2004 to 2005, 259 hospitalized children less than five years of age were studied and divided in two groups: those with healthcare-associated diarrhea and those without healthcare-associated diarrhea. Diarrhea was considered to be healthcare-associated if diarrhea developed at least three days after admission. Eighty-four (32.4%) of the children had nosocomial diarrhea. Among those with nosocomial diarrhea, formula-fed babies were significantly more likely to be cases than breast-fed babies. Among those with nosocomial diarrhea, those with dirty food containers, dirty clothes or bed sheets, pacifiers were significantly more likely to be infected than children with clean belongings and no pacifiers. Based on swab samples, the most contaminated modes of transmission were hands (74%), stethoscopes (14%), and oral cavities (12%). The three most common bacteria found from healthcare workers' hands or belongings were *Enterobacter* species, *Citrobacter* species, and *Proteus* species.[35]

In the United States, an analysis was done of *Clostridium difficile* infections and infection control.[36] *Clostridium difficile* is a pathogen that quickly spreads through contact transmission. It is more common in healthcare facilities than in the community because of the relationship between antimicrobial therapy and *C.difficile* infection. After enhanced infection control measures, rates of *C.difficile* infections decreased. The enhanced infection control measures included: automatically placing patients with diarrhea into contact precautions until *C.difficile* was ruled-out, requiring bleach-based cleaning products, and requiring healthcare workers to wash their hands with soap and water, instead of gel, before caring for the patient.[36]

Prevention of Healthcare-Associated Infections

Most HAI prevention strategies rely on access to water, sanitation, and/or hygiene. The most important preventive method is hand hygiene.[37] Hand hygiene compliance is a problem in both high-income and low/middle-income countries.[37] In low- and middle-income countries, high priority is placed on hand hygiene programs.[37] A review cited 22 studies using with hand-hygiene campaigns in low- and middle-income countries. Out of the 22 studies, 18 supported the theory that hand hygiene campaigns decrease HAIs.[37]

Other methods to prevent HAIs are proper use of personal protective equipment, safe use and disposal of sharps, safe handling and disposal of waste, safe management of laundry (soiled linens), food hygiene, maintenance of a clean environment, decontamination of equipment, and staff personal hygiene.[37] Some of the common methods used for treatment and disposal of healthcare wastes in low- and middle-income countries include autoclaves, microwaves, chemical disinfection, combustion, and ground disposal at dump sites, controlled landfills, pits, and sanitary landfills.[38] The type of waste determines the appropriate method of treatment and disposal.[38]

A bachelor's thesis was written on a case-study of a West African hospital ward's compliance to the above precautions, evaluated through observation and interviews.[39] HCWs were not 100% compliant with hand hygiene, mainly only washing their hands after completing procedures while using a common towel to dry their hands. Gloves were not always worn or replaced between procedures.

Sharps were thrown out with the regular wastes and were not protected to prevent needlesticks. Infectious wastes were not separated from regular wastes. Dirty laundry was separated from clean laundry, but there was no standard for handling dirty laundry. Data was not collected on food hygiene. The ward was cleaned three times a day, but furniture was not cleaned regularly and the floors were often soiled with body fluids. Equipment was not usually cleaned when used between patients and surgical blades were sometimes re-used. The hospital did not have rules on how to manage the cleaning of HCW's clothes, but a neat appearance was required.[39] These findings support the need for improved knowledge and compliance with infection control practices in low- and middle-income countries.

Recent Initiatives to Reduce HAIs

The morbidity, mortality, and costs of HAIs have encouraged some organizations to improve infection control in health care facilities. Therefore, the new post-2015 Sustainable Development Goals are not the only priorities that will impact HAIs. For example, in the United States, 80% of all HAIs are due to surgical site infections, catheter-associated urinary tract infections, central venous catheter-related bloodstream infections, and ventilator-associated pneumonia. Thus, the Centers for Medicare and Medicaid Services (CMS) now require hospitals to decrease or limit the incidences of those certain infections in order to obtain reimbursements for Medicare and Medicaid.[40]

The World Health Organization (WHO) World Alliance for Patient Safety brought together nineteen clinicians, researchers, and policy makers from low- and middle-income, transitional, and high-income countries in all seven WHO regions.[41] They decided on 50 different research priorities on various topics for low- and middle-income countries using a three stage modified Delphi process and ranked them. Research on healthcare-associated infections was ranked number six out of the 50 research priorities.[41]

The WHO has two main patient safety projects related to HAIs – 1) Clean Care is Safer Care and 2) Safe Surgery Saves Lives.[42] The WHO encourages each country's Ministry of Health to adopt these global patient safety challenges in their country's health care facilities. The Clean Care is Safer Care challenge aims to address infection control in all healthcare facilities.[42] Hand hygiene is a large component of the challenge. The Safe Surgery Saves Lives challenge aims to prevent adverse events due to surgical procedures.[42] The WHO developed guidelines on safe surgery and objective 6 focuses on methods to minimize the risk of surgical site infections. Activities from both campaigns may decrease healthcare-associated infections and medical errors.[42]

Conclusion

There is limited information on HAI in low- and middle-income countries, as a whole. There is even less information on HAI in the low- and middle-income countries in South and East Asia. Some countries have published data on HAI prevalence and/or incidence, but there is no single document that summarizes the burden of HAIs for the low- and middle-income countries in Asia. Many high-income countries have their own established surveillance system. For instance, Europe had the Hospitals in Europe Link for Infection Control through Surveillance (HELICS) and the Improving Patient Safety in Europe (IPSE) network, which merged to now become the European Centre for Disease Prevention and Control (ECDC). The organization conducts continuous surveillance of healthcare-associated infections from surgical site infections and in intensive care units. They also recently started performing point-prevalence surveys on HAIs to include other types of HAIs.[43] As for low- and middle-income countries, there is a systematic review on HAIs in Sub-Saharan Africa[12] and one on low- and middle-income countries, as a whole[10].

HAI surveillance systems, particularly on bloodstream infections, are mostly found in high-income countries, such as the U.S., Canada, England, Germany, Japan, and Australia.[44] The International Nosocomial Infection Control Consortium (INICC) performs HAI surveillance in the following countries: Argentina, Bolivia, Brazil, Bulgaria, China, Colombia, Costa Rica, Croatia, Cuba, Czech Republic, Dominican Republic, Ecuador, Egypt, El Salvador, Greece, India, Italy, Iran, Jordan, Kosovo, Lebanon, Lithuania, Macedonia, Malaysia, Mexico, Morocco, Nigeria, Pakistan, Panama, Peru, Philippines, Poland, Puerto Rico, Romania, Saudi Arabia, Serbia, Singapore, Slovakia, Sri Lanka, Sudan, Thailand, Tunisia, Turkey, Uruguay, Venezuela, and Vietnam.[45]

More research is needed on HAI in South and East Asia, on HAI in low- and middle-income countries, and on the link between WASH and HAI. As the burden of HAI continues and multi-drug resistant organisms spread, research can help determine priorities and actions needed to decrease the burden and to slow or stop the spread. This systematic review will help organize the current studies available in low- and middle-income countries of South and East Asia by presenting HAI prevalence data while also highlighting the link between WASH and HAIs.

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Chapter 3: Manuscript

Water-, Sanitation-, and Hygiene-Based Healthcare-Associated Infections
in the Low- and Middle-Income Countries of South and East Asia:
A Systematic Review

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Contribution of Student

Data collection through PubMed, EMBASE, and MOH websites.
Writing of manuscript.
Analysis of prevalence (healthcare-associated infections, type of infections, pathogens, potential WASH-based modes of transmission linked to pathogen, potential types of infections linked to pathogen).
All figure and table development.

Abstract

Water-, Sanitation-, and Hygiene-Based Healthcare-Associated Infections
in the Low- and Middle-Income Countries of South and East Asia:
A Systematic Review

By Stephanie Belbis

Background
Low- and middle-income countries have a high burden due to healthcare-associated infections, which may be prevented with proper water, sanitation, and hygiene.

Aim
To review the prevalence of water, sanitation, and hygiene-based healthcare-associated infections and pathogens in the low- and middle-income countries in South and East Asia

Methods
A systematic review was conducted using English PubMed and EMBASE articles published between 2000 and 2014 about the prevalence of healthcare-associated infections in the low- and middle-income countries in South and East Asia. Information on the types of healthcare-associated infections and pathogens was also collected.

Findings
Twelve articles met the inclusion criteria and were included in this review. The reported prevalence of healthcare-associated infections in the low- and middle-income countries of South and East Asia ranged from 3.53% to 33.33%. The most common type of healthcare-associated infections reported in these studies was respiratory tract infections with a prevalence ranging from 24.0 to 65.2%. The most common pathogens implicated with healthcare-associated infections included *Acinetobacter baumannii, Enterococcus* spp., *Escherichia coli*, *Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Staphylococcus aureus*. All pathogens linked to healthcare-associated infections were related to water, sanitation, and hygiene.

Conclusion
The low- and middle-income countries in South and East Asia are affected by healthcare-associated infections that are transmitted through water, sanitation, and hygiene. Further surveillance studies, particularly in rural hospitals, are needed in each country to provide a better estimate of the prevalence of healthcare-associated infections in low- and middle-income countries.

Introduction

Healthcare-associated infections (HAIs) are a major cause of morbidity and mortality, and a significant economic burden to patients and the health care system worldwide, particularly in low- and middle-income countries.[1] The reported prevalence of healthcare-associated infections in low- and middle-income countries is 15.5 per 100 patients[1] while the prevalence in Europe and the U.S. ranges from 5 to 15 per 100 patients.[2] In Europe, HAIs are responsible for an extra 25 million days of hospitalization yearly,[3] and in low- and middle-income countries, each case of HAI increases a hospital length of stay by 6 to 23 days in non-ICU medical wards.[4] The excess cost per healthcare-associated infections varies by country and by type of infection. In the United States, the excess cost of a hospital stay due to device- and procedure-related HAI ranges from $589 - $25,546 per case.[5] In low- and middle-income countries, there is limited information on excess cost due to HAIs.[4]

In low- and middle-income countries, the focus on the prevention of HAIs is growing.[6] Proper water, sanitation, and hygiene facilities and practices are known to help prevent HAIs, in general.[7] The recent Ebola situation in West Africa has also highlighted patient and occupational safety issues, often associated with HAIs, by promoting safe sanitation and hygiene practices to slow the spread of Ebola.[8] Furthermore, the post-2015 Sustainable Development Goals include universal access to basic water, adequate sanitation and adequate handwashing facilities in health centers in Goal 6 to "ensure availability and sustainable management of water and sanitation for all."[9]

Healthcare-associated infections are those acquired through interactions with healthcare facilities and medical procedures. The Centers for Disease Control and Prevention (CDC) has developed case definitions for HAIs in general and specific types of HAIs. The CDC defines HAIs as infections that meet the following criteria:

1) Presence of a localized or systemic condition due to an infectious agent(s) or its toxin(s).

2) No evidence of infection present or incubating during the time of admission to the hospital.[10]

The World Health Organization defines a hospital-acquired infection as "an infection acquired in hospital by a patient who was admitted for a reason other than that infection."[11]

The CDC also defines various categories of healthcare-associated infections, such urinary tract infections, bloodstream infections, pneumonia, ventilator-associated events, surgical site infections, gastrointestinal infections, and skin and soft tissue infections.[12]

HAI surveillance in low- and middle-income countries is significantly limited, particularly in Asia. No systematic review has studied burden of HAIs in Asian low- and middle-income countries. Low- and middle-income countries are defined by the World Bank as countries with a gross national income per capita of less than $12,746.[13] In the regions of East Asia/Pacific and South Asia, the low- and middle-income countries include American Samoa, Cambodia, China, Fiji, Indonesia, Kiribati, the Democratic People's Republic of Korea, Laos, Malaysia, the Marshall Islands, Micronesia, Mongolia, Myanmar, Palau, Papua New Guinea, the Philippines, Samoa, the Solomon Islands, Thailand, Timor-Leste, Tuvalu, Tonga, Vanuatu, Vietnam, Afghanistan, Bangladesh, Bhutan, India, the Maldives, Nepal, Pakistan, and Sri Lanka.

Understanding the modes of HAI transmission help prioritize interventions and inform appropriate steps to prevent HAIs. The pathogens can be transmitted through the air, water, food, surface contact, medications, medical devices, medical wastes, humans, or animals.[14] This study focuses on pathogens that can be transmitted through poor water, sanitation, and hygiene.

The goal of this study is to describe the current status of HAIs in the low- and middle-income countries of South and East Asia by providing a review of studies from this region that report the prevalence of HAIs. Furthermore, the study will examine available information on the prevalence of the various types of infections and pathogens commonly found in healthcare settings and the potential modes of water-, sanitation-, and hygiene-related transmissions.

Methods

Sample Population

Surveillance studies were found through PubMed and EMBASE. Other reports were searched through each South and East Asian country's Ministry of Health websites.

Data Collection

Searches on PubMed, EMBASE, and Ministry of Health websites were conducted during December 2014 to January 2015. Keywords used included the name of the country, "healthcare-associated infection," "healthcare associated infection," "health care associated infection," "hospital infection," "hospital acquired infection," "nosocomial," "cross infection [Mesh]," and "prevalence."

Articles were included if they were written in English; were published between January 2000 and December 2014; addressed infection, not colonization, in the low- and middle-income countries of South and East Asia; and described the prevalence of HAIs using the following equation:

$$\frac{\text{Number of patients with a healthcare-associated infection during the study period}}{\text{Total number of patients in the hospital or unit during the study period}}$$

From each article that met the criteria for inclusion, the prevalence of the type of HAIs was collected if the prevalence of the type of HAI was calculated using the following equation:

$$\frac{\text{Number of patients with the type of healthcare-associated infection during the study period}}{\text{Total number of patients with any healthcare-associated infection during the study period}}$$

In addition, from each article that met the inclusion criteria, information on the prevalence of HAI-based pathogens was extracted if the prevalence of the pathogen was calculated using the following equation:

$$\frac{\text{Number of positive HAI isolates growing the specific pathogen during the study period}}{\text{Total number of positive HAI isolates growing any pathogen during the study period}}$$

The prevalence of the types of HAIs from the included articles was analyzed if the prevalence of the type of HAI was provided in at least three of the included studies to highlight the most common types of HAIs. The prevalence of HAI-linked pathogens from the included articles was analyzed if the prevalence of the HAI-linked pathogen was provided in at least two of the included studies to highlight the most common pathogens. Pathogens were also linked to known modes of transmission specific to water, sanitation (enteric pathogens), hand hygiene, medical devices, and airborne/droplets. Pathogens were also linked to known types of infections.

Ethical Approvals

As this systematic review analyzed published articles, it was not considered human subject research, and Emory IRB approval was not required.

Results

The initial search in PubMed and EMBASE identified 2825 articles. No reports or articles were found through Ministry of Health websites and no reviews were identified from the Cochrane Library. The titles and abstracts of the 2825 articles were reviewed. During this step, 2775 articles were excluded because the titles and abstracts did not address the research question on the prevalence of HAIs. These articles were also excluded if they were duplicates, resulting in 50 remaining articles. The full text articles were screened for these 50 articles to determine prevalence rates of HAIs, as calculated using the equation above. Twelve articles met the full inclusion criteria (Figure 1).[15-26] Six articles described hospital studies in China,[16-18,20,22-23] two in India,[19,24] and one each in Cambodia,[15] Malaysia,[21] Indonesia,[25] and Mongolia.[26] Eight of the articles were point-prevalence studies,[15,17,18,20,21,22,25,26] three were prospective surveillance studies,[16,19,24] and one was a retrospective cohort study over four years.[23] Two of the prospective surveillance studies analyzed data over an 18-month period[19,24] and the other prospective surveillance study analyzed data over an eight year period.[16] Seven studies evaluated patients throughout all units of the hospital.[17-18,20-22,25-26] Three studies evaluated pediatric or neonatal patients,[15,16,23] and one of these focused on the neonatal intensive care unit.[23] Three studies evaluated patients in the intensive care unit,[19,24] and one of these was in the neonatal intensive care unit[23] and another was in the respiratory intensive care unit (Table 1).[24]

Healthcare-associated infections

The overall HAI prevalence from these 12 articles ranged from 3.5% to 33.3%.[15-26] For the studies that monitored whole hospital data [excluding studies monitoring only pediatric/neonatal units or only intensive care units (ICUs)], the HAI prevalence range was 3.5% to 13.9%.[17-18,20-22,25-26] In the studies that only included pediatric or neonatal patients, the prevalence ranged from 8.3% to 13.8%.[15,16,23] In studies that focused on intensive care unit patients only, the range was 8.8% to 33.3% (Table 2).[19,24]

Types of healthcare-associated infections

Some studies included information on the prevalence of various types of HAIs and the pathogens related to the HAIs. Eight studies had prevalence data on the types of HAIs.[16,17,21-26] Of these eight studies, two articles only included pediatric or neonatal patients[16,23] and two articles focused on patients in intensive care units (Table 1).[23-24] One article about neonatal intensive care patients was included in both the pediatric/neonatal and the intensive care categories.[23] The prevalence of the types of HAIs that were provided in at least three of the eight articles are presented in this review. These types of infections include respiratory tract infections (RI),[16,17,22,26] pneumonia (PNA),[21,23,24] surgical site infections (SSI),[17,22,42,51] bloodstream infections (BSI),[16,17,21-26] urinary tract infections (UTI),[16,17,21-26] gastrointestinal infections (GI),[16,17,21,22] and skin and soft tissue infections (SSTI).[16,17,22]

Respiratory infections, specifically pneumonia, were the most prevalent of HAIs in all, except one, article. In that article, SSIs were the most common HAIs and RIs were not mentioned.[25] Outside of RIs, three articles indicated that the most prevalent type of HAI was SSI,[17,22,25] two articles showed the most prevalent HAI was BSI,[23,24] two articles reported UTI as the most common type of HAI,[21,26] and one article pointed to GI (Table 1).[16]

Healthcare-Associated Respiratory Tract Infections

The overall prevalence of RI described in four articles ranged from 24.0% to 65.2%.[16,17,22,26] In the article studying only the pediatric populations, the prevalence was 65.2%.[16] When the article with only the pediatric population only was excluded, the prevalence ranged from 24.0% to 63.2%.[17,22,26]

Pneumonia

Three articles further specified the type of infection, looking at PNA.[21,23,24] The prevalence of PNA from three articles ranged from 20.r% to 59.7%.[21,23,24] The prevalence reported in the pediatric only article was 56.8%.[23] The prevalence of PNA was 20.4% to 59.7% when excluding the pediatric only article.[21,24]

Surgical-Site Infections

The overall prevalence of SSI from four articles ranges from 9.60% to 41.46%.[17,22,25,26] No pediatric/neonatal or intensive care only articles mentioned SSI.[16,23,24]

Bloodstream Infections

The overall prevalence of BSI from eight articles ranges from 1.15 to 31.71%.[16,17,21-26] The prevalence using two pediatric/neonatal only studies ranges from 7.87% to 24.50%[16,23] while the prevalence using two intensive care unit only studies ranges from 19.48% to 24.50%.[23,24] Excluding the pediatric/neonatal only and the intensive care only studies, the prevalence range is the same as the overall prevalence range of BSI.[17,21,22,25,26]

Urinary Tract Infections

The overall prevalence of UTI from eight articles ranges from 1.44% to 24.00%.[16,17,21-26] The prevalence using two pediatric/neonatal only studies ranges from 1.44% to 6.74%[16,23] while the prevalence of using two intensive care unit only studies ranges from 1.44% to 3.90%.[23,24] Excluding the pediatric/neonatal only and the intensive care unit only studies, the prevalence of UTI ranges from 4.60% to 24.00%.[17,21,22,25,26]

Gastrointestinal Tract Infections

The overall prevalence of GI from four studies ranges from 1.94% to 11.24%.[16,17,21,22] The prevalence from the pediatric only study is 11.24%.[16] Excluding the pediatric only study, the prevalence of GI ranges from 1.94% to 9.20%.[17,21,22]

Skin and Soft Tissue Infections

The overall prevalence of SSTI ranges from 3.24% to 8.99%.[16,17,22] In the pediatric only study, the prevalence is 8.99%.[16] Excluding the pediatric only study, the prevalence of SSTI ranges from 3.24% to 6.90% (Table 3).[17,22]

Pathogens

Eight articles had prevalence data on pathogens isolated from HAIs.[15-19,22-24] Of these eight articles, three only included pediatric or neonatal patients[15,16,23] and three only included patients in intensive care (Table 1).[19,23,24] One article on HAIs regarding neonatal intensive care patients was included in both the pediatric/neonatal and the intensive care categories.[23] The pathogens that were described in at least two of the eight articles include *Acinetobacter baumannii,*[16-18,22,23] *Acinetobacter* species,[19,24] *Burkholderia/Pseudomonas cepacia*,[17,23] *Candida albicans,*[22,23] *Candida* species,[19,24] *Candida* *tropicalis,*[22,23] *Enterobacter aerogenes,*[22,23] *Enterobacter cloacae,*[16,37] *Enterococcus* species,[16,17,19,22] *Escherichia coli,*[16,17,18,19,22,23,24] *Haemophilus influenza,*[16,23] *Klebsiella pneumoniae,*[16-19,22-24] *Klebsiella pneumoniae* – extended spectrum beta-lactamase (ESBL) producing,[15,23] *Morganella morganii,*[19,23] *Pseudomonas aeruginosa,*[15-19,22-24] *Staphylococcus aureus,*[15,18,19,23] *Staphylococcus aureus* – methicillin resistant,[15,17,24] *Staphylococcus epidermidis,*[16,17,22,23] *Stenotrophomonas maltophilia,*[17,22,23] and *Streptococcus pneumoniae* (Table 1).[17,23]

For each of the eight articles with pathogen information, the 19 pathogens identified in this review were ranked in order of their prevalence. The op three pathogens found to be in the top three most common pathogens in at least one of the articles reviewed include *Acinetobacter baumannii* (2 articles),[18,23] *Enterococcus* species (1 article),[19] *Escherichia coli* (5 articles),[16-18,22,24] *Klebsiella pneumoniae* (4 articles[8,17,19,23] - 5 articles when including ESBL-producing *Klebsiella pneumoniae*),[23] *Pseudomonas aeruginosa* (7 articles),[15-19,22,24] and *Staphylococcus aureus* (1 article).[15] Six out of the eight articles indicated that *Pseudomonas aeruginosa* was the most common pathogen detected in HAIs[16-19,22,24] while two articles show *Klebsiella pneumoniae* as the most common pathogen.[15,23]

Prevalence of Pathogens

The prevalence of *Acinetobacter baumannii* in positive isolates of HAIs ranged from 7.6% and 23.3%. The prevalence of *Burkholderia/Pseudomonas cepacia* ranged from 0.4% to 6.0%, *Candida albicans* ranged from 0.8% to 7.1%, *Candida* species ranged from 4.4% to 6.4%, *Candida tropicalis* ranged from 1.1% to 1.6%, *Enterobacter aerogenes* ranged from 1.7% to 2.7%, *Enterobacter cloacae* ranged from 2.6% to 7.7%, *Enterococcus* species ranged from 4.5% to 11.4%, *Escherichia coli* ranged from 2.7% to 15.4%, *Haemophilus influenzae* ranged from 0.4% to 3.8%, *Klebsiella pneumoniae* ranged from 2.2% to 26.4%, *Klebsiella pneumoniae* (ESBL-producing) ranged from 14.0% to 36.7%, *Morganella morganii* ranged from 0.4% to 0.5%, *Pseudomonas aeruginosa* ranged from 7.4% to 26.9%, *Staphylococcus aureus* ranged from 1.2% to 10.0%, *Staphylococcus aureus* (methicillin-resistant) ranged from 2.0% to 8.7%, *Staphylococcus epidermidis* ranged from 2.0% to 4.0%, *Stenotrophomonas maltophilia* ranged from 4.3% to 6.0%, and *Streptococcus pneumoniae* ranged from 0.4% to 2.0% (Table 4).

Pathogens and Transmission

The pathogens isolated from the HAIs reported in these studies can be transmitted via poor water, sanitation, and hygiene conditions. All of the most commonly reported HAI pathogens can be transmitted through improper hand hygiene and unsterile medical devices. All of them, except for *Staphylococcus aureus*, have been shown to be transmitted via water.[27-30] Out of the most common pathogens, *Enterococcus* species, *Escherichia coli,* and *Klebsiella pneumoniae* are sanitation-related as faecal pathogens.[31] *Acinetobacter baumannii* and *Staphylococcus aureus* are known to spread through the air or droplets.[14]

The pathogens that are transmissible through water include *Acinetobacter baumannii,*[27] *Burkholderia/Pseudomonas cepacia,*[27] *Enterobacter aerogenes,*[28] *Enterobacter cloacae,*[28] *Enterococcus* species,[29] *Escherichia coli,*[30] *Klebsiella pneumoniae,*[28] *ESBL-producing Klebsiella pneumoniae,*[28] *Pseucomonas aeruginosa*,[27] and *Stenotrophomonas maltophilia*.[27]

Enteric pathogens include *Enterobacter aerogenes,*[31] *Enterobacter cloacae,*[31] *Enterococcus* species,[29] *Escherichia coli,*[31] *Klebsiella pneumoniae,*[31] *ESBL-producing Klebsiella pneumoniae,*[31] and *Morganella morganii*.[31]

Pathogens that can be transmitted through improper hand hygiene include *Acinetobacter baumannii*,[32] *Burkholderia/Pseudomonas cepacia,*[32] *Candida albicans,*[32] *Candida* species,[32] *Candida tropicalis,*[32] *Enterobacter aerogenes,*[31] *Enterobacter cloacae,*[31] *Enterococcus* species,[29] *Escherichia coli,*[31] *Klebsiella pneumoniae,*[32] ESBL-producing *Klebsiella pneumoniae,*[32] *Morganella morganii,*[31] *Pseudomonas aeruginosa,*[32] *Staphylococcus aureus,*[32] methicillin-resistant *Staphylococcus aureus,*[32] *Staphylococcus epidermidis,*[32] and *Stenotrophomonas maltophilia.*[33]

Pathogens that can be transmitted through the use of medical devices in the hospital are the same as those transmitted by dirty hands – *Acinetobacter baumannii*,[34] *Burkholderia/Pseudomonas cepacia,*[14] *Candida albicans,*[14] *Candida* species*,*[14] *Candida tropicalis,*[14] *Enterobacter aerogenes,*[31] *Enterobacter cloacae,*[31] *Enterococcus* species*,*[29] *Escherichia coli,*[31] *Klebsiella pneumoniae,*[31] ESBL-producing *Klebsiella pneumoniae,*[31] *Morganella morganii,*[31] *Pseudomonas aeruginosa,*[14] *Staphylococcus aureus,*[34] methicillin-resistant *Staphylococcus aureus,*[34] *Staphylococcus epidermidis,*[35] and *Stenotrophomonas maltophilia.*[33]

The pathogens that can be spread through respiratory modes – airborne or droplet – include *Acinetobacter baumannii,*[14] *Haemophilus influenza,*[36] *Staphyloccus aureus,*[14] methicillin-resistant *Staphylococcus aureus,*[14] and *Streptococcus pneumoniae* (Table 4)*.* [36]

Pathogens and Infection

Table 5 lists the pathogens analyzed in this review and the known infections that the pathogen can cause to further explain the burden of each pathogen. The pathogens linked to infections include *Acinetobacter baumannii*,[37] *Burkholderia/Pseudomonas cepacia*,[38] *Candida albicans*,[39] *Candida* species,[40] *Candida tropicalis*,[41] *Enterobacter aerogenes,*[42] *Enterobacter cloacae*,[42] *Escherichia coli,*[44,45] *Haemophilus influenzae,*[46] *Klebsiella pneumoniae*,[47] *Klebsiella pneumoniae* – ESBL-producing,[47] *Morganella morganii*,[48] *Pseudomonas aeruginosa,*[49] *Staphylococcus aureus*,[50] *Staphylococcus aureus* – methicillin-resistant,[50] *Staphylococcus epidermidis*,[51,52] *Stenotrophomonas maltophilia*,[53] and *Streptococcus pneumoniae.*[54] Many of these pathogens can cause a variety of infections.

Discussion

Healthcare-associated infections cause a major burden to healthcare facilities around the world. No other review has looked specifically at the prevalence of HAIs in the low- and middle-income countries of South and East Asia. Our study is an overview of HAIs in the region's low- and middle-income countries.

Prevalence of HAI

Various studies have examined the prevalence of HAIs in low- and middle-income countries. One review ofHAIs in low- and middle-income countries showed an overall prevalence range of 7.2% to 21.6%.[6] Another review article showed an pooled prevalence of 15.5% in low- and middle-income countries.[1] One review article focused specifically on HAIs in Africa, in which all countries are considered low- and middle-income by the World Bank. The reported HAI prevalence ranged between 2.5% and 14.8%.[55] All of these results are similar to, or within the range reported here (3.53% to 13.94%) for adults. A review article that evaluated studies analyzing neonatal infections in low- and middle-income countries reported a HAI range of 1.8% to 13.0%.[56] An article reviewed in our study evaluating neonates had a similar prevalence at 8.80%.[23]

The prevalence estimates for high-income countries ranged from 4.5% to 7.1%.[2] Because our study's prevalence has a wider range (3.53% to 33.33%) than the range for high-income countries, it is difficult to adequately compare the results with the high-income countries' results.

One recent review article compiled prevalence data in high-income and low/middle-income countries of Southeast Asia and resulted in a pooled prevalence of overall HAIs of 9.0%,[58] which also falls within the range of our study. This is expected, since the recent review article included the low- and middle-income countries of Indonesia, Malaysia, the Philippines, Thailand, and Vietnam, and only contained studies from one high-income country - Singapore.[57]

Prevalence of Types of Infections

As for types of infections, the results of our study show a higher prevalence of respiratory tract infections, compared to the other types of infections. A review of low- and middle-income countries worldwide differs from our study's results as the most common healthcare-associated infections were surgical-site infections.[1] A review of African HAIs also focused more on surgical-site infections.[56] Only articles addressing all types of HAIs were included in our study. Thus, articles addressing only surgical-site infections were excluded and the prevalence data from those articles were not considered in our study results.

Prevalence of Pathogens

The most common pathogens found in our review were *Acinetobacter baumannii, Enterococcus* species*, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Staphylococcus aureus*.

A review of worldwide low- and middle-income countries showed that the most common pathogens in high-risk patients were enterobacteriaceae (excluding *Escherichia coli*), in mixed populations were *Staphylococcus aureus*, in surgical-site infections were enterobacteriaceae (excluding *Escherichia coli*), in ventilator-associated and health-care-associated pneumonia were *Pseudomonas* species, and in bloodstream infections were *Staphylococcus aureus*.[1]

Our study did not determine which pathogens were the most common in each type of infection, in high-risk patients, and in mixed populations, so we cannot directly compare our results with this review. Also in our study, the total prevalence of enterobacteriaceae is unknown. Enterobacteriaceae incorporate a group of gram-negative pathogens.[58] Some of the most common enterobacteriaceae include *Escherichia coli, Klebsiella* species, *Enterobacter* species, *Salmonella,* and *Shigella.*[58] Our study included the prevalence for *Escherichia coli, Klebsiella,* and *Enterobacter* separately. *Klebsiella* was found to be the most common pathogens in two articles reviewed, which are also pediatric and neonatal patients only articles.[15,23] Thus, enterobacteriaceae is an important group of pathogens included our study, but the total prevalence was not determined and cannot be directly compared with the review of HAIs in low- and middle-income countries worldwide.

All of these most common pathogens have modes of transmissions related to water, sanitation, and hygiene (Table 4) and can lead to a variety of infections (Table 5).

Antimicrobial Resistance

Additional concern is with drug-resistant pathogens, predominantly ESBL-producing *Klebsiella pneumoniae* and methicillin-resistant *Staphylococcus aureus*, both of which were one of the most common pathogens in our study when added to their antimicrobial susceptible counterparts. *Klebsiella pneumoniae* was the most common pathogen in two articles included in our study, which also looked only at pediatric and neonatal patients.[15,23]

In Asia, growing antimicrobial resistance is a priority.[59] In a 2013 review of Asian countries, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant Enterococci, and carbapenem-resistant Enterobateriaceae (CRE) were found. The review mainly obtained data from Singapore, a high-income country, but it is geographically close to some low- and middle-income Asian countries, so possible spread of drug-resistant pathogens is a concern.[59] In particular, the World Health Organization has recognized the seriousness of CRE, especially carbapenem-resistant *Klebsiella*, since it was found in all WHO regions.[60] Carbapenem is already used as a last line available antibiotic treatment for *Klebsiella*, meaning that there is no known and established antibiotic that would treat carbapenem-resistant *Klebsiella*.[60] Newer and more expensive antibiotics treat drug-resistant pathogens, as a whole, so low- and middle-income countries with may lack the resources to treat them as resistance continues to grow.

Study Limitations

Studies on HAIs, in general, have some inevitable limitations. First, infection may not occur in every patient exposed to a pathogenic microorganism. Some patients are only colonized with the pathogen and do not exhibit signs and symptoms of an infection. Various factors, such as patient age and immune function, may increase the risk of infections. So although transmission may be high, patients within the facility may have strong enough immune function to prevent an infection.

Second, patients who are discharged before the infections are diagnosed would be missed in the surveillance of HAI. Obtaining information on discharged patients would be a challenge if the patients do not seek medical care for their infection or possibly obtain medical care at another hospital.

Finally, facilities may use different laboratory methods and brands of diagnostic equipment to detect certain pathogens. The methods may have varying sensitivities and specificities, affecting the reported prevalence of each pathogen.

Notwithstanding, there are some weaknesses in our study that can be overcome. For example, only a small number of articles were analyzed in our study. Including only English articles from PubMed and EMBASE may have limited the number of articles. This likely affects the reported prevalence estimates. Also, most of the articles looked at prevalence of HAI in urban hospitals. Eight of the articles are in urban settings,[15-17,19-21,23,26] three are unknown,[18,24,25] and one comprises both urban and rural hospitals.[22] Adding rural data would provide a better insight to infections in the region.

The articles also have different case definitions of HAIs and the types of HAIs. Six of the articles used the Centers of Disease Control and Prevention (CDC) definition,[17,20,21,23,25,26] four used a locally-modified CDC definition,[15,16,22,24] and two did not describe how an HAI was defined.[18,19] Having a standardized case definition may give a different prevalence.

Conclusion

Further studies are suggested to enhance the knowledge of HAIs in the low- and middle-income countries of South and East Asia. More surveillance programs, particularly in rural areas and other countries without published material, is recommended. Furthermore, the results from the surveillance programs would need to be published for future reviews. A more comprehensive review that includes articles on specific types of infections can give a better estimate of the prevalence of the types of infection. The addition of studies on incidence rates can also enhance the information of HAIs in the region. Further studies of the quality of hospital water, waste management, hand hygiene, respiratory hygiene, and medical equipment is recommended.

The findings of our study support some public health recommendations for health care facilities, such as the importance of hand hygiene. More focus is encouraged on contact precautions – proper hand hygiene and the use of sterile medical devices – to prevent the spread of the most common pathogens in health care facilities.

Tables and Figures

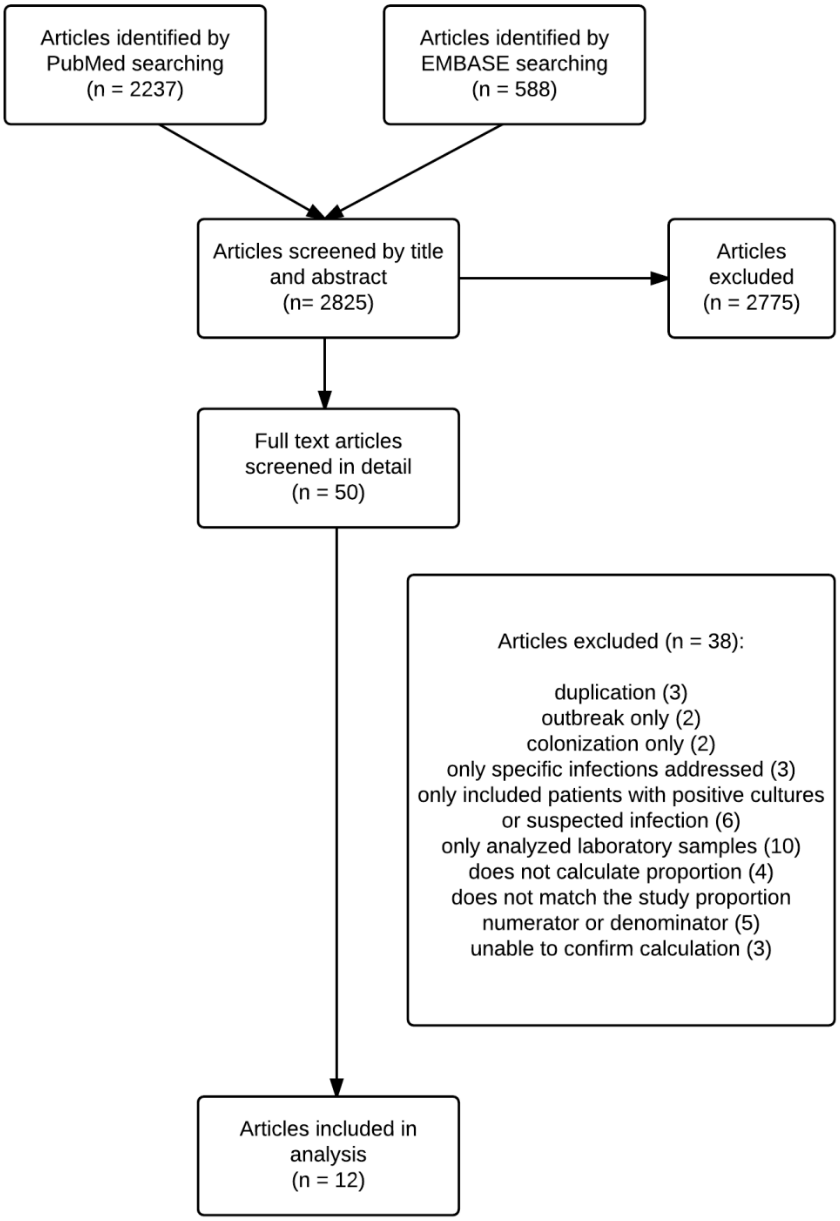

Figure 1: Search strategy of articles and results

Table 1: Characteristics of studies on healthcare-associated infection prevalence in the low- and middle-income countries of South andEast Asia

Authors, Year	Country	Study Design	Hospital Setting	Time Period	Number of Patients	Infection Types	Pathogens	HAI Prevalence
Stoesser, N., et.al., 2013 [15]	Cambodia	point-prevalence	One pediatric Hospital	Jan. 2011 - Dec. 2011	428	-	Major pathogens: *K. pneumoniae* (ESBL-producing), *P. aeruginosa, S. aureus, S. aureus* (methicillin-resistant) Minor pathogens: *Klebsiella* species, imipenem-resistant *Pseudomonas aeruginosa*	13.79%
Zhang, Q., et.al., 2010 [16]	China	prospective surveillance (8 years)	Pediatric nephrology unit of one hospital	May 2000 - May 2008	971	Major: BSI, GI, RI, SSTI, UTI Minor: None	Major pathogens: *A. baumannii, E. cloacae, Enterococcus* spp., *E. coli, H. influenzae, K. pneumoniae, P. aeruginosa, S. epidermidis* Minor pathogens: *Bacillus proteus, Streptococcus viridans*	8.34%
Tao, X., et.al., 2014 [17]	China	point-prevalence	All inpatient units of one hospital	Nov. 13, 2013	2,434	Major: BSI, GI, RI, SSTI, SSI, UTI Minor: Central Nervous System Infections	Major pathogens: *A. baumannii, B. cepacia, Enterococcus* spp., *E. coli, K. pneumoniae, P. aeruginosa, S. aureus* (methicillin-resistant), *S. epidermidis, S. maltophilia, S. pneumoniae* Minor pathogens: none	3.53% (18.39% for ICU only)
Li, C., et.al., 2014 [18]	China	point-prevalence	All inpatient units of multiple	Jan. 2010 - Dec. 2010	407,208	-	Major pathogens: *A. baumannii, E. coli, K. pneumoniae, P. aeruginosa, S.*	3.60%

			hospitals				*aureus* Minor pathogens: none	
Datta, P., et.al., 2014 [19]	India	prospective surveillance (18 months)	Intensive care unit in one hospital	May 1, 2010 - Oct. 31, 2011	679	-	Major pathogens: *Acinetobacter* spp., *Candida* spp., *Enterococcus* spp., *E. coli, K. pneumoniae, M. morganii, P. aeruginosa, S. aureus* Minor pathogens: none	24.44%
Li, H., et.al., 2013 [20]	China	point-prevalence	All inpatient units of one hospital	Dec. 26, 2011	2,511	-	-	7.89%
Hughes, A.J., 2005 [21]	Malaysia	point-prevalence	All inpatient units of one hospital	July 16 - 17, 2011	538	Major: BSI, GI, PNA, UTI Minor: Clinical Sepsis, Deep Surgical Site, Superficial Surgical Site	-	13.94%
Xie, D., et.al.,2010 [22]	China	point-prevalence	All inpatient units of multiple hospitals	Nov. 2007 - Nov. 2008	20,350	Major: BSI, GI, RI, SSTI, SSI, UTI Minor: None	Major pathogens: *A. baumannii, C. albicans, C. tropicalis, E. aerogenes, Enterococcus* spp., *E. coli, K. pneumoniae, P. aeruginosa, S. aureus, S. epidermidis, S. maltophilia* Minor pathogens: viruses, *Mycobacterium* species, *Proteus* species, respiratory syncytial virus, rotavirus, *Serratia* species, *Streptococcus* species	3.88%

Xu, X., et.al., 2010 [23]	China	retrospective cohort (4 years)	Neonatal intensive care unit of one hospital	Jan. 2005 - Dec. 2008	3,942	Major: BSI, PNA, UTI Minor: Central Line-Associated Bloodstream Infections, Meningitis, Ventilator-Associated Pneumonia, Enteritis, Conjunctivitis, Pleuritis	Major pathogens: *A. baumannii, B. cepacia, C. albicans, C. tropicalis, E. aerogenes, E. cloacae, E. coli, H. influenzae, K. pneumoniae, K. pneumoniae* (ESBL-producing), *M. morganii, P. aeruginosa, S. aureus, S. epidermidis, S. maltophilia, S. pneumoniae* Minor pathogens: *Acinetobacter lwoffii, Candida mycoderma, Candida parapsilosis, Enterococcus faecium, Flavobacterium indologenes, Flavobacterium meningosepticum, Klebsiella ornithinolytica, Pseudomonas alcaligenes, Staphylococcus auricularis, Staphylococcus capitis, Staphylococcus haemolyticus, Staphylococcus sciuri, Staphylococcus sciuri, Staphylococcus simulans, Staphylococcus warneri, Streptococcus mitis*	8.80%
Agarwal, R., et.al., 2006 [24]	India	prospective surveillance (18 months)	Respiratory intensive care unit of one hospital	Jul. 2002 - Dec. 2003	201	Major: BSI, PNA, UTI Minor: Clinical Sepsis, Central Line-Associated Bloodstream Infections, *C.difficile* colitis	Major pathogens: *Acinetobacter* spp., *Candida* spp., *E. coli, K. pneumoniae, P. aeruginosa, S. aureus* (methicillin-resistant) Minor pathogens: *Alcaligenes faecalis,* methicillin-susceptible *Staphylococcus aureus, Staphylococcus auricularis, Staphylococcus capitis, Staphylococcus haemolyticus, Staphylococcus sciuri, Staphylococcus simulans, Staphylococcus warneri, Streptococcus mitis*	33.33%

Duerink, D.O., et.al., 2006 [25]	Indonesia	point-prevalence	All inpatient units of multiple hospitals	Aug. 2001, Oct. 2001, Feb. 2002, Sept 2008	2,222	Major: BSI, SSI, UTI Minor: Clinical Sepsis, Deep, Organ Space, and Superficial Surgical Site Infection	-	3.69%
Ider, B.E., et.al., 2010 [26]	Mongolia	point-prevalence	All inpatient units of multiple hospitals	Sept. 2008	933	Major: BSI, RI, SSI, UTI Minor: None	-	5.36%
ICU = Intensive Care Unit; BSI = Bloodstream Infection; GI = Gastrointestinal Infection; PNA = Pneumonia; RI = Respiratory Tract Infection;								
SSTI = Skin and Soft Tissue Infection; SSI = Surgical Site Infection; UTI = Urinary Tract Infection								
Major types of infections = Types of healthcare-associated infections in which the prevalence was provided in the article and included in our analysis. Types of infections were included in our analysis if the prevalence was provided in at least three of the articles reviewed.								
Minor types of infections = Types of healthcare-associated infections in which the prevalence was provided in the article but excluded from our analysis.								
Major pathogens = Pathogens in which the prevalence was provided in the article and included in our analysis. Pathogens were included in our analysis if the prevalence was provided in at least two of the articles reviewed.								
Major pathogens = Pathogens in which the prevalence was provided in the article but were excluded from our analysis.								

Table 2: Prevalence of healthcare-associated infections

	Healthcare-associated infection prevalence range (%)
All articles	3.53 - 33.33
Excluding pediatric/neonatal units and intensive care units only	3.53 - 13.94
Pediatric/Neonatal units only	8.34 - 13.79
Intensive care units only	8.80 - 33.33

Table 3: Prevalence of the types of healthcare-associated infections

	All (%)	Pediatric/Neonatal *only* (%)	Intensive Care Unit *only* (%)	Excluding pediatric/neonatal only and intensive care unit only articles (%)
Respiratory Tract Infections*	24.00 - 65.16	65.16	-	24.00 - 63.15
Pneumonia	20.39 - 59.74	56.80	-	20.39 – 59.74
Surgical Site Infections	9.60 - 41.46	-	-	9.60 – 41.46
Bloodstream Infections	1.15 - 31.71	7.87 - 24.50	19.48 - 24.50	1.15 – 31.71
Urinary Tract Infections	1.44 - 24.00	1.44 - 6.74	1.44 - 3.90	4.60 - 24.00
Gastrointestinal Infections	1.94 - 11.24	11.24	-	1.94 - 9.20
Skin and Soft Tissue Infections	3.24 - 8.99	8.99	-	3.24 - 6.90

**Most common type of healthcare-associated infection in every article, except one.*

Table 4: Prevalence of the healthcare-associated infection pathogens and the likely modes of transmission

	Prevalence Range (%)	Likely Modes of Transmission				
		Water	Sanitation (fecal pathogens)	Improper Hand Hygiene	Medical Devices	Airborne /Droplet
Acinetobacter baumannii*	7.65 - 23.29	x[27]		x[32]	x[34]	x[14]
Burkholderia cepacia/ Pseudomonas cepacia	0.39 - 6.00	x[27]		x[32]	x[14]	
Candida albicans	0.78 - 7.08			x[32]	x[14]	
***Candida* species**	4.35 - 6.39			x[32]	x[14]	
Candida tropicalis	1.13% - 1.56			x[32]	x[14]	
Enterobacter aerogenes	1.70 - 2.71	x[28]	x[31]	x[31]	x[31]	
Enterobacter cloacae	2.55 - 7.69	x[28]	x[31]	x[31]	x[31]	
Enterococcus* species	4.53 - 11.42	x[29]	x[29]	x[29]	x[29]	
Escherichia coli*	2.71 - 15.38	x[30]	x[31]	x[31]	x[31]	
Haemophilus influenza	0.39 - 3.84					x[14]
Klebsiella pneumoniae*	2.17 - 26.36	x[28]	x[31]	x[32]	x[31]	
***Klebsiella pneumoniae,* ESBL-producing**	13.95 - 36.67	x[28]	x[31]	x[32]	x[31]	
Morganella morganii	0.39 - 0.46		x[31]	x[31]	x[31]	
Pseudomonas aeruginosa*	7.36 - 26.94	x[27]		x[32]	x[14]	
Staphylococcus aureus*	1.16 - 10.00			x[32]	x[34]	x[14]
***Staphylococcus aureus,* methicillin-resistant**	2.00 - 8.70			x[32]	x[34]	x[14]
Staphylococcus epidermidis	1.98 - 4.00			x[32]	x[35]	
Stenotrophomonas maltophilia	4.25 - 6.00	x[27]		x[33]	x[33]	
Streptococcus pneumoniae	0.39 - 2.00					x[36]

**top three most common pathogens in least one of the articles reviewed*

Pathogens with the high-end of the prevalence range at >10%.

Pathogens with the high-end of the prevalence range at 5-10%.

Pathogens with the high-end of the prevalence range at <5%.

Table 5: Pathogens and Known Infections Caused by Pathogen

Pathogen	Infections
Acinetobacter baumannii	bacteremia, pneumonia, meningitis, urinary tract infection, wound infection[37]
Burkholderia cepacia/ Pseudomonas cepacia	bacteremia, urinary tract infection, septic arthritis, peritonitis, respiratory tract infection[38]
Candida albicans	gastrointestinal infection, vaginitis, pyelonephritis, peritonitis, candidemia, meningitis, hepatosplenic infection[39]
Candida species	gastrointestinal infection, urinary tract infection, respiratory tract infection[40]
Candida tropicalis	candidemia, urinary tract infection[41]
Enterobacter aerogenes	cerebral abscess, pneumonia, meningitis, septicemia, wound infection, urinary tract infection, abdominal cavity/intestinal infections[42]
Enterobacter cloacae	same as *Enterobacter aerogenes*[42]
Enterococcus species	endocarditis, pelvic infection, urinary tract infection, [gastrointestinal tract colonization][43]
Escherichia coli	hemolytic uremic syndrome, hemorrhagic colitis,[44] enteritis, urinary tract infection, septicemia, neonatal meningitis[45]
Haemophilus influenza	pneumonia[46]
Klebsiella pneumoniae	urinary tract infection, pneumonia, septicemia, soft tissue infection[47]
Klebsiella pneumoniae, ESBL-producing	same as *Klebsiella pneumoniae*[47]
Morganella morganii	healthcare-associated infection case reports of septicemia, post-operative diabetic foot infection[48]
Pseudomonas aeruginosa	pneumonia, skin and soft tissue infection, bacteremia, ventilator-associated pneumonia, urinary tract infection[49]
Staphylococcus aureus	skin infection, endocarditis, pneumonia, osteomyelitis[50]
Staphylococcus aureus, methicillin-resistant	same as *Staphylococcus aureus*[50]
Staphylococcus epidermidis	diabetic foot osteomyelitis,[51] bacteremia in infants and children[52]
Stenotrophomonas maltophilia	respiratory tract infection – including pneumonia, bacteremia, skin and soft tissue, osteomyelitis, meningitis, urinary tract infection, endophthalmitis[53]
Streptococcus pneumoniae	respiratory tract infection, bloodstream infection, central nervous system infection[54]

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Chapter 4: Conclusion and Recommendations

Healthcare-associated infections are a problem in the low- and middle-income nations in South and East Asia. From our systematic review of HAIs in low- and middle-income countries of South and East Asia, the prevalence of HAI in whole hospitals ranges from 3.5% to 13.9% with the prevalence higher in the ICU at 8.8% to 33.3%. We also found respiratory tract infections to be the most frequently reported type of healthcare-associated infection. Bloodstream infections are also common, particularly in intensive care units. The usual pathogens observed in these infections include *Acinetobacter baumannii, Enterococcus* spp., *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa,* and *Staphylococcus aureus*. Special concern is with the growing drug-resistant pathogens, particularly ESBL-producing *Klebsiella pneumoniae* and methicillin-resistant *Staphylococcus aureus.* These pathogens related to these infections are often spread through poor water, sanitation, and hygiene and result in a wide range of infections.

Research Implications

Recommendations to Improve This Review

Search Strategy

If this review is repeated, a more comprehensive search would be helpful in enhancing the prevalence estimates. Non-English studies and unpublished data can be used. It may be useful to reach out to each country's Ministry of Health to see if they have unpublished surveillance data that can be included. Including prevalence data from articles addressing only certain types of infections and specific pathogens would be helpful in obtaining more prevalence data on the HAI subsets.

Surveillance

Our review only included 12 articles, and more published surveillance results would help give a more accurate result in the prevalence of HAIs, types of HAIs, and pathogens. More healthcare-associated infection surveillance programs should be developed in hospitals in the area, especially in rural hospitals. Rural areas are known to have fewer resources (infrastructure/supplies, human, and monetary) available for hospital quality improvement.[1] The majority of the articles in the review only addressed hospitals in urban settings. As surveillance programs are being developed, there should be a consensus among countries for standardized case study definitions, data collection, and calculations. Finally, these surveillance results should be published for access to the prevalence results.

Additional Research Topics Measuring HAIs

Incidence

To better understand the magnitude of HAIs in the region, other methods can be studied. Incidence rates, which are calculated using time, can be analyzed. This is typically seen as number of infections per patient-days. Patient-days is the total number of patients in a hospital in a specific time period.[2] Regarding equipment-based healthcare-associated infections, incidence can be shown as number of infections per equipment-days. Equipment-days is the number of days the patient uses the equipment.[2] Common equipment analyzed for healthcare-associated infections are ventilators, urinary catheters, and central lines.[3]

Outpatients

Outpatients can also be studied to determine HAIs. Patients may go home after being infected by a healthcare-associated pathogen without realizing they are infected. In common HAI surveillance methods, discharged patients are not included. Certain pathogens, such as the human immunodeficiency virus, may not quickly manifest while the patient is in the healthcare facility, may not be routinely tested in healthcare facilities, and may be poorly documented regarding its transmission.[4]

Looking at the prevalence and the incidence of HAI from clinics and from follow-up appointments may be helpful in understanding the magnitude of HAIs.

Healthcare Workers

Healthcare workers can also be studied to understand the spread of HAIs. With the amount of time healthcare workers spend in healthcare facilities exposed to infectious patients, they seem to be at high risk for transmission of pathogens. However, because they generally have better immune systems than hospitalized patients, these pathogens may not cause infection in healthcare workers. Studies on colonization of pathogens may give a better idea of the spread of the pathogen.

Other Pathogens

Studies on other healthcare-associated pathogens that are not commonly identified in low- and middle-income countries would be helpful. *Clostridium difficile* is a sanitation-based HAI pathogen in many high-income countries due to prior antibiotic use, but is not commonly seen in low- and middle-income countries.[5] *Clostridium difficile* results in diarrhea,[6] which is a common symptom due to various pathogens in low- and middle-income countries.[7] Low- and middle-income countries would need resources to establish an accurate diagnosis of the cause of diarrhea, which include an extensive understanding of the patient history, stool cultures, fecal pH, small bowl and rectal biopsies, and other stool studies.[7] Using this list of diagnostic tools to confirm diagnosis can a challenge for low- and middle-income countries if resources are not readily available.

Legionellosis is a water-based HAI pathogen causing outbreaks in many low- and middle-income countries due to the hospital infrastructure with the water system, such as hot water tanks, cooling systems, and towers.[8] Because of the nature of transmission, it is not expected to be found in limited resource areas that do not have extensive water systems, but studies to actively testing for *Legionella* in low- and middle-income countries may be helpful to understand true presence or absence of the disease in low- and middle-income countries.

Additional Research Topics on HAIs

Policies

A complete compilation of regional, national, and local recommendations to prevent HAIs in the low- and middle-income countries of South and East Asia can be developed. These recommendations include guidelines, laws, and regulations. The guidelines and regulations would include topics on water quality, water access, sanitation access, sanitation management, solid waste care management, hand hygiene, medical device sterilization, medical device use techniques, personal protective equipment access, and personal protective equipment quality. A description of how well the guidelines and laws/regulations are enforced in each region, country, province, or city/town may be helpful. A search of policies and enforcements would be helpful when including information in the local language and unpublished information from the Ministry of Health and other healthcare facility law enforcement agencies.

Behavior

Although there may be guidelines and regulations, it is ultimately up to the people in the healthcare facilities to prevent the spread of HAIs. A behavioral study on health care workers, patients, and visitors regarding water, sanitation, and hygiene techniques would be valuable. This is also called a KAP study, evaluating knowledge, attitudes, and practices. Knowledge is the awareness of 1) HAIs, 2) the spread of HAIs, and 3) the means of how to prevent spread. Attitudes are the beliefs surrounding the issue. Practices are the performance of the actions taken to prevent spread of HAIs. Currently, studies have been done on the prevalence of hand hygiene campaigns in low- and middle-income countries. A review found 22 studies in low- and middle-income countries using hand hygiene to decrease healthcare-associated infections.[9] Understanding the health care worker knowledge, attitudes, and practice of hand hygiene may help further evaluate the use of hand hygiene campaigns. More studies are needed on other techniques, such as medical device sterilization, regular room cleaning, and proper use of personal protective equipment.

Environmental Impact

Research on the actions of healthcare facilities that affect the external community would be useful. One idea is to study the impact of the facility infrastructure on the surrounding community. Studies can look at how the waste water leaving the health care facilities affect the environment and if the management of waste water is correlated with community-acquired infections. Through this type of study, interventions can be done to prevent negative effects on the nearby area.

Studies can also look at the behaviors of discharged patients, visitors, and healthcare workers outside of the healthcare facilities. This can help describe the potential spread of pathogens from healthcare facilities to the external community via humans. Tests for colonization can be performed.

Programming implications

Education

Adequate education on proper water-, sanitation-, and hygiene-activities is important for healthcare workers, patients, and visitors. Education for healthcare workers should include everyone who works in the facility even if they do not have direct contact with patients. Physicians, specifically, should be trained to accurately diagnose HAIs. This can help catch potential facility-specific issues quickly.

From this study, particular education is needed to limit contact-based transmission, the spread of fecal pathogens, and the prevalence of healthcare-associated respiratory tract infections. To prevent contact-based transmission, education would focus on hand hygiene, use of personal protective equipment, and use of medical devices. To limit the spread of fecal pathogens, education should be on proper water access, the management of water quality, evaluation of quantity and quality of latrines, hand hygiene, use of personal protective equipment, and the handling of medical equipment. To decrease the rate of healthcare-associated respiratory tract infections, special education should be on personal protective equipment.

Innovations

Procedures

Based on this study, new innovations to prevent contact-based transmission, the spread of fecal pathogens, and healthcare-associated respiratory tract infections are needed. Current healthcare facility procedures, such as the way vital signs are checked, may need to be evaluated. Studies should be done to evaluate the impact of a myriad of healthcare facility procedures on HAIs. Innovative ideas on hospital procedures that could limit contact time and exposure to pathogens may be helpful to decrease HAIs.

Technology

Innovative technology that can limit contact time and exposure to pathogens can help decrease healthcare-associated infections. In low- and middle-income countries, these technological advances should be low-cost.

Policy & Economic implications

National and local policies throughout the region should be designed and implemented to support the use of the World Health Organization guidelines, if not already available. WHO guidelines helpful in decreasing HAIs using appropriate WASH techniques include: [10]

- Infection prevention and control guidance for care in patients in health-care settings, with focus on Ebola, August 2014

- Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care, WHO guidelines, April 2014
- WHO guidelines on hand hygiene in health care, August 2009
- WHO policy on TB infection control in health-care facilities, congregate settings, and households
- Infection prevention and control in health care for confirmed or suspected cases of pandemic (H1N1) 2009 and influenza-like illnesses, 2009.
- Core components for infection prevention and control programmes, 2008
- WHO Aide – memoire: Standard infection control precautions in health care, 2006
- Prevention of hospital-acquired infections, 2nd edition. A practical guide, 2002

Extra focus is suggested on contact transmission, sanitation, and respiratory tract HAIs, based on our review. Facilities must adhere to those policies. Enforcement should occur on a national and a local level. National and local governments should be responsible for creating, maintaining, and enforcing the policies in each licensed or public health care facility.

To support research, programs, and policies, investment in HAI prevention, particularly in the low- and middle-income countries, is of utmost importance. Due to the high burden of HAIs in low- and middle-income countries, prevention may cost less than treatment.

Conclusion

Although this study is a systematic review of available articles on healthcare-associated infections in the low- and middle-income countries of South and East Asia, more studies and more surveillance are needed to better understand the current prevalence of HAIs, types of HAIs, and pathogens linked to the HAIs in the region.

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