World Health Organization

Patient Safety

A World Alliance for Safer Health Care

Report on the Burden of Endemic Health Care-Associated Infection Worldwide

Clean Care is Safer Care

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Report on the Burden of Endemic Health Care-Associated Infection Worldwide

A systematic review of the literature

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Developed by the Clean Care is Safer Care Team (Patient Safety Programme - Innovation, Information, Evidence and Research Cluster).

Clean Care is Safer Care Team:
Benedetta Allegranzi, Sepideh Bagheri Nejad, Gabriela Garcia Castillejos, Claire Kilpatrick, Edward Kelley, Elizabeth Mathai.
External lead: Didier Pittet.

Content contribution
Lead author:
Benedetta Allegranzi
WHO Patient Safety Programme, Geneva, Switzerland

Critical technical contribution
Sepideh Bagheri Nejad
WHO Patient Safety Programme, Geneva, Switzerland
Didier Pittet
WHO Collaborating Centre on Patient Safety
University of Geneva Hospitals and Faculty of Medicine, Geneva, Switzerland

Technical contribution
Marie-Noëlle Chraiti
WHO Collaborating Centre on Patient Safety
University of Geneva Hospitals and Faculty of Medicine, Geneva, Switzerland

Statistical Analysis
Christophe Combescure
Division of Clinical Epidemiology
University of Geneva Hospitals and Faculty of Medicine, Geneva, Switzerland
Homa Attar
WHO Collaborating Centre on Patient Safety
University of Geneva Hospitals and Faculty of Medicine, Geneva, Switzerland

Reviewers
Najeeb Al Shorbaji
WHO Patient Safety Programme, Geneva, Switzerland
Edward Kelley
WHO Patient Safety Programme, Geneva, Switzerland
Colin Mathers
WHO Mortality and Burden of Disease, Geneva, Switzerland

Editor
Rosemary Sudan
Freelance editor

Figures
Laurens Zwakhals
WHO Public Health Information and Geographic Information Systems, Geneva, Switzerland

ABBREVIATIONS

BSI	bloodstream infection
CDC	Centers for Disease Control and Prevention
CL	central line
CR-BSI*	catheter-related bloodstream infection
CR-UTI	catheter-related urinary tract infection
ECDC	European Centre for Disease Prevention and Control
EPIC	European Prevalence of Infection in Intensive Care
HAP	health care-associated pneumonia
HCAI	health care-associated infection
HELICS	Europe Link for Infection Control through Surveillance
HIV	human immunodeficiency virus
ICU	intensive care unit
INICC	International Nosocomial Infection Control Consortium
SSI	surgical site infection
NNIS	National Nosocomial Infection Surveillance System
NHSN	National Healthcare Safety Network
USA	United States of America
UTI	urinary tract infection
VAP	ventilator-associated pneumonia
WHO	World Health Organization

* CR-BSI is used as a generic term throughout the report when referring to different categories included in the retrieved articles, e.g. “central venous catheter-associated”, “central venous catheter-related”, “central line-associated”, or “catheter-related bloodstream infection”.

SUMMARY

Health care-associated infection (HCAI) is acquired by patients while receiving care and represents the most frequent adverse event. However, the global burden remains unknown because of the difficulty to gather reliable data. In many settings, from hospitals to ambulatory and long-term care, HCAI appears to be a hidden, cross-cutting problem that no institution or country can claim to have solved yet. HCAI surveillance is complex and requires the use of standardized criteria, availability of diagnostic facilities and expertise to conduct it and interpret the results. Surveillance systems for HCAI exist in several high-income countries but are virtually nonexistent in most low- and middle-income countries.

Data included in this report are the results of systematic reviews of the literature on endemic HCAI from 1995 to 2010 in high- and low/middle-income countries. According to published national or multicentre studies, pooled HCAI prevalence in mixed patient populations was 7.6% in high-income countries. The European Centre for Disease Prevention and Control (ECDC) estimated that 4 131 000 patients are affected by approximately 4 544 100 episodes of HCAI every year in Europe. The estimated HCAI incidence rate in the USA was 4.5% in 2002, corresponding to 9.3 infections per 1000 patient-days and 1.7 million affected patients.

The systematic review of the literature revealed clearly an extremely fragmented picture of the endemic burden of HCAI in the developing world. Only very scanty information was available from some regions and no data at all for several countries (66%). Many studies conducted in health-care settings with limited resources reported HCAI rates higher than in developed countries. Hospital-wide prevalence of HCAI varied from 5.7% to 19.1% with a pooled prevalence of 10.1%. Of note, the pooled HCAI prevalence was significantly higher in high- than in low-quality studies (15.5% vs 8.5%, respectively). Surgical site infection (SSI) is the most surveyed and most frequent type of infection in low- and middle-income countries with incidence rates ranging from 1.2 to 23.6 per 100 surgical procedures and a pooled incidence of 11.8%. By contrast, SSI rates vary between 1.2% and 5.2% in developed countries.

The risk of acquiring HCAI is significantly higher in intensive care units (ICUs), with approximately 30% of patients affected by at least one episode of HCAI with substantial associated morbidity and mortality. Pooled cumulative incidence density was 17.0 episodes per 1000 patient-days in adult high-risk patients in industrialized countries. By contrast, the incidence of ICU-acquired infection among adult patients in low- and middle-income countries ranged from 4.4% up to 88.9% and pooled cumulative incidence density was 42.7 episodes per 1000 patient-days.

High frequency of infection is associated with the use of invasive devices, in particular central lines, urinary catheters, and ventilators. Among adult ICU patients in high-income countries, pooled cumulative incidence densities of catheter-related BSI (CR-BSI), urinary catheter-related UTI (CR-UTI), and ventilator-associated pneumonia (VAP) were 3.5 per 1000 CL-days, 4.1 per 1000 urinary catheter-days, and 7.9 per 1000 ventilator-days, respectively. In low- and middle-income countries, pooled cumulative incidence densities of CR-BSI, CR-UTI, and VAP were 12.2 per 1000 CL-days, 8.8 per 1000 urinary catheter-days, and 23.9 per 1000 ventilator-days, respectively. Newborns are also a high-risk population in developing countries and neonatal infection rates are three to 20 times higher than in industrialized countries.

The impact of HCAI implies prolonged hospital stay, long-term disability, increased resistance of microorganisms to antimicrobials, a massive additional financial burden for health systems, high costs for patients and their families, and excess deaths. In Europe, HCAIs cause 16 million extra-days of hospital stay, 37 000 attributable deaths, and contribute to an additional 110 000 every year. Annual financial losses are estimated at approximately € 7 billion, including direct costs only. In the USA, approximately 99 000 deaths were attributed to HCAI in 2002 and the annual economic impact was estimated at approximately US$ 6.5 billion in 2004. Information is again very scanty from low- and middle-income countries and no data are available at national or regional levels. According to a report on device-associated infections in 173 ICUs from 25 countries in Latin America, Asia, Africa, and Europe, crude excess mortality in adult patients was 18.5%, 23.6%, and 29.3% for CR-UTI, CR-BSI, and VAP, respectively. A review of several studies showed that increased length of stay associated with HCAI varied between 5 and 29.5 days.

Although HCAI global estimates are not yet available, by integrating data from published studies, there is clear evidence that hundreds of millions of patients are affected every year worldwide, with the burden of disease much higher in low- and middle-income countries. There is an urgent need to establish reliable systems for HCAI surveillance and to gather data on the actual burden on a regular basis. Evaluation of the key determinants of HCAI is an essential step to identify strategies and measures for improvement. Robust evidence exists that HCAI can be prevented and the burden reduced by as much as 50% or more. Solid recommendations have been issued by national and international organizations, but their application needs to be strengthened and accompanied by performance monitoring both in high-income and low- and middle-income countries. HCAI must be treated as a priority patient safety issue within comprehensive approaches to be tackled effectively. The WHO Patient Safety programme integrates efforts with other WHO programmes to reduce HCAI by assisting with the assessment, planning, and implementation of infection prevention and control policies, including timely actions at national and institutional levels.

INTRODUCTION

Health care-associated infections (HCAIs) are infections that patients acquire while receiving treatment for medical or surgical conditions and are the most frequent adverse event during care delivery.[1] HCAI is a major problem for patient safety and its impact can result in prolonged hospital stay, long-term disability, increased resistance of microorganisms to antimicrobial agents, a massive additional financial burden for the health system, high costs for patients and their families, and excess deaths.[2,3] The risk to acquire HCAI is universal and pervades every health-care facility and system worldwide, but the true burden remains unknown in many nations, particularly in developing countries.

Data on the burden of diseases worldwide are regularly published by the World Health Organization (WHO) to inform health-care workers, policy-makers, and the public of the most important diseases in terms of morbidity and mortality.[4] HCAI does not appear on the list of over 100 diseases evaluated. The most likely reason is that the diagnosis of HCAI is complex and relies on multiple criteria and not on a single laboratory test. In addition, national systems of continuous surveillance are seldom in place. In many settings, from hospitals to ambulatory and long-term care, HCAI appears to be a hidden, cross-cutting problem that no institution or country can claim to have solved yet.

This report presents the evidence available from the scientific literature on the endemic burden of the most frequent types of HCAI and provides an assessment of epidemiological differences among countries according to income levels. The report aims also to identify major obstacles and gaps to assess the magnitude of the HCAI burden worldwide and to identify solutions and future perspectives for improvement. All data presented were compiled from systematic reviews of studies published in the scientific literature from 1995 to 2010. Methods and key definitions used are described in Boxes 1 and 2.

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Box 1

Methodology used for systematic reviews and analysis included in this report

Type of infection
Overall HCAI, health care-associated urinary tract infection (UTI), surgical site infection (SSI), hospital-acquired pneumonia (HAP), ventilator-associated infection (VAP), and health care-associated bloodstream infection (BSI).

Sources
PubMed, Cochrane Library, World Health Organization (WHO) regional medical databases (Appendix). A comprehensive list of search terms (Appendix) including MeSH terms “cross infection”, “infection control”, “developing countries” and “developed countries” was used, together with the individual names of high-, middle- and low-income countries.

Inclusion criteria
All studies reporting full or partial data related to infection rates, risk factors, mortality, excess length of stay, costs, HCAI aetiology in general, and health care-associated UTI, BSI, SSI, and HAP/VAP. For high-income countries, only national or multicentre studies were included.

Exclusion criteria
Duplicate references and publications reporting the same data; studies reporting outbreaks; studies including community-acquired infections.

Time limits
January 1995 to December 2010.

Language
No language restrictions.

Criteria to define high-quality studies
prospective design; use of standardized definitions (i.e. according to the USA CDC NHSN system);[5] detection of at least all four major infections for studies related to HCAI in general; and publication in a peer-reviewed journal.

Statistical analysis
Descriptive statistics of data retrieved from high, low- and middle-income countries were performed; studies were classified according to patient population (adult, neonatal and paediatric), level of risk (high-risk patients, i.e. those admitted to ICUs, burn and transplant recipients vs mixed patient populations, including patients admitted to other lower-risk areas), and type of infection (overall HCAI, including at least the four most frequent infections, UTI, SSI, BSI, and HAP/VAP). Data pooling was performed by using meta-analytical techniques.

Box 2

Epidemiological definitions used in this report

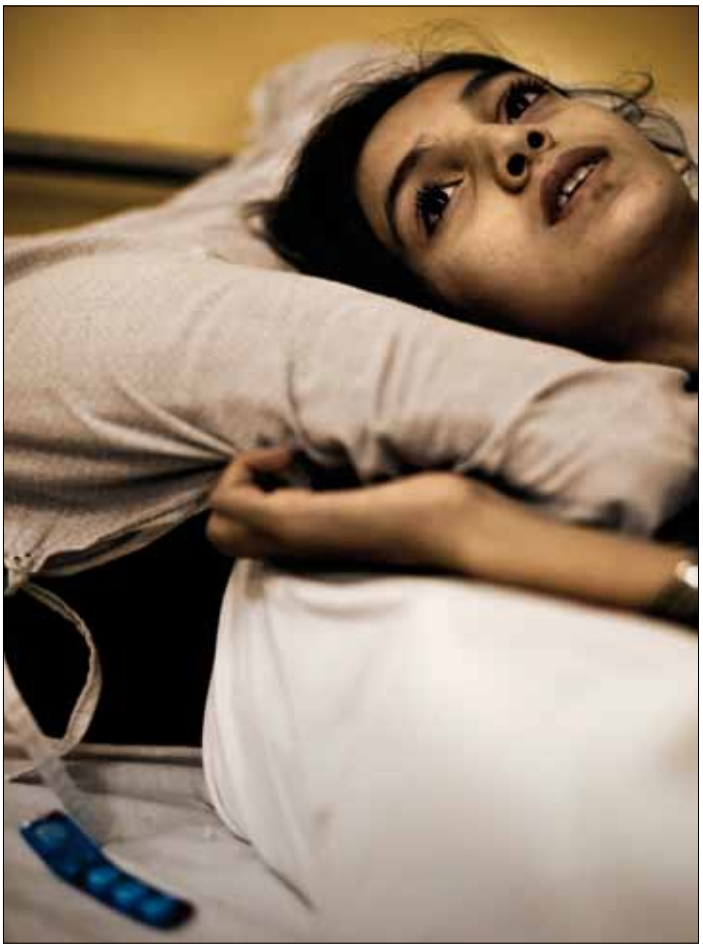
HCAI prevalence
Number of infection episodes or infected patients per 100 patients present in the health-care setting or ward at a given point in time.

HCAI incidence
Number of new infection episodes or new patients acquiring an infection per 100 patients followed up for a defined time period. Periods vary according to the patient population. For SSI, it is usually 30 days after surgery (1 year in the case of prosthesis or implant), whereas it refers to the duration of hospital or ward stay for other infections.

HCAI incidence density
Number of infection episodes per 1000 patient-days or device-days.

Developed countries
High-income countries according to the World Bank classification 2009.[6]

Developing countries
Low- and middle-income countries according to the World Bank classification 2009.[6]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1.

Health care-associated infection in different settings and risk factors

HCAI is defined as: “An infection occurring in a patient during the process of care in a hospital or other health-care facility which was not present or incubating at the time of admission. This includes infections acquired in the hospital, but appearing after discharge, and also occupational infections among staff of the facility”.[7] Given this definition and before focusing on epidemiological data, it is important to scrutinize the issue of HCAI in depth, to identify how it can be related to different types of health-care settings, and to determine the factors leading to an increased risk of transmission of health care-associated pathogens and of infection onset.

Most studies reporting data on the burden of endemic HCAI were conducted in acute-care settings and in high-income countries. However, an increasing body of evidence has highlighted the epidemiological differences in non-acute care settings and in low- and middle-income countries. The modern evidence-based approach to infection prevention and control clearly emphasizes that no type of health-care facility in any country can claim to be free from the risk of HCAI.

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The term “HCAI” has replaced the former ones used to refer to such infections, i.e. “nosocomial” or “hospital” infection, as evidence has shown that this event can affect patients in any settings where they receive care. Only scanty data exist on the burden of HCAI outside hospitals because the culture of infection prevention and control and the systems for the surveillance of these events are inexistent or poorly developed in these settings. For instance, many patients probably acquire respiratory infections while seeking care for other diseases and waiting in ambulatory care facilities, especially in overcrowded settings in developing countries, or during epidemic periods. As the patient returns to the community, it is almost impossible to identify the occurrence of an infection acquired while accessing a primary care facility. Although no systematic data are available on the epidemiology of HCAI in primary and secondary care, the need for a targeted approach to infection control in these settings has been highlighted[8] and specific recommendations have been issued in some countries, e.g. in England.[9]
Home care has also become highly prevalent. For example, in 1996 in the USA, 8 million patients received care at home; of these, 774 113 had at least one indwelling medical device, mostly intravascular.[10] HCAI is no longer restricted to basic hospital care as in the past and now requires the implementation of specific infection control measures in other settings.

Due to longer life expectancy and social dynamics, an increasing number of individuals in high-income countries are nursed in residential homes for the elderly, but little is known about the burden of HCAI in these settings. Several projects on infection control in long-term care facilities have been initiated in Europe over the last five years.[11] Accumulated evidence suggests that any

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resident living in these facilities develops one to three infections per year on average, most frequently urinary tract infection (UTI) and pneumonia. It was also demonstrated that the onset of infection represents the most common cause of hospital admission and death for residents in long-term care facilities, mainly from pneumonia.[12,13]

Risk factors for HCAI vary according to the type of health-care facility and to the care area where the patient is admitted, and are partially different in developing countries. In studies conducted hospital-wide in high-income countries, the most common factors independently associated with HCAI occurrence were: age >65 years; admission as an emergency and to the intensive care unit (ICU); hospital stay longer than seven days; placement of a central venous catheter, indwelling urinary catheter, or an endotracheal tube; undergoing surgery; trauma-induced immunosuppression; neutropenia; a rapidly or ultimately fatal disease (according to the McCabe-Jackson classification); and impaired functional or coma status.[14-18] The same risk factors were identified in acute-care settings in low- and middle-income countries with the addition of other determinants that are more broadly associated with poverty, such as a lack of basic hygiene and limited resources. These include malnutrition, age < 1 year, low birth weight, parenteral nutrition, or two or more underlying diseases.[19-28] Although not demonstrated as independent risk factors, general barriers to optimal infection control practices in low- and middle-income countries are lack of financial support, inadequate numbers of trained personnel working in infection control, understaffed hospital units, and insufficient equipment and supplies.[3]

2.

Methods and challenges of health care-associated infection surveillance

Most HCAIs become evident 48 hours or more following admission (typical incubation period).[5] Infection may present also after patient discharge. In these cases, the patient has become colonized or infected while in hospital, but the pathogen incubation period exceeds the patient's hospital stay. For instance, several studies report that over 50% of surgical site infections (SSI) manifest post-discharge.[29-38]

HCAI may be caused by infectious agents from endogenous or exogenous sources. Endogenous sources are body sites, such as the skin, nose, mouth, gastrointestinal tract, or vagina, that are normally colonized by local microbial flora. These microorganisms can become invasive under certain favourable conditions and/or cause infection when they contaminate sterile sites. Transmission to these sites occurs most frequently via health-care workers' hands.[39] Exogenous sources are those external to the patient, such as health-care workers, visitors, patient care equipment, medical devices, or the health-care environment. HCAIs are not restricted only to patients; health-care workers, ancillary staff, and visitors can also be affected.

HCAIs occur both as part of an endemic (ongoing) trend within a health-care facility or as epidemic situations, i.e. when new cases in a given population and during a given period substantially exceed what is expected, based on local endemic data. The endemic situation and occurrence of outbreaks in a health-care setting are important indicators of the quality and safety of patient care. For this reason, surveillance is at the heart of infection prevention and control. Surveillance is defined as "the ongoing, systematic collection, analysis, and interpretation of health data essential to the planning, implementation and evaluation of public health practice, closely integrated with the timely dissemination of these

data to those who need to know".[40] Surveillance activities are an essential tool to reduce HCAI as they are the important first step in identifying problems and priorities. Furthermore, it has been shown that conducting prospective surveillance activities, especially if prolonged, help to raise awareness of the problem and, finally, to decrease infection rates.[41-43]

The use of standardized definitions is crucial to the reliability of HCAI surveillance. These allow to establish that the infection was acquired during hospital stay, to ascertain that the condition is a true infection and not a colonization (i.e. the presence of microorganisms on skin or mucous membranes, in open wounds, or in excretions/secretions, but without any overt adverse clinical signs or symptoms) or contamination (i.e. the exceptional and accidental presence of microorganisms in normally sterile body sites or fluids that does not reflect actual infection status), and to define the type of infection according to the body site. The most reliable definitions are those issued by the USA National Nosocomial Infections Surveillance (NNIS) system and recently revised by the National Healthcare Safety Network (NHSN)[5]. The application of standardized definitions is one of the minimum requirements for data comparisons at local, national, and international levels, although other variables need to be taken into account to allow appropriate benchmarking.

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The use of these definitions requires the evaluation of clinical evidence collected from a review of the patient chart or other clinical records and/or the performance of microbiologic tests and/or direct observation of the infection site, e.g. surgical wound, catheter insertion site, etc.[5] Further evaluation of diagnostic investigations or clinical information by a physician or a surgeon may be necessary (e.g. direct observation during a surgical operation, endoscopic examination) for the application of some criteria defining HCAI. These requirements lead to an accurate diagnosis in most cases, but make surveillance a resource-demanding activity. In settings where electronic patient records and automated systems exist, combining this information with the use of specific software or databases greatly simplifies HCAI surveillance. In settings with limited resources, these systems are usually lacking, medical and nurse records are often not well organized and detailed, and access to laboratory and radiological facilities is very limited and frequently of low quality. In addition, in low- and middle-income countries, a lack of expertise in the field of infection prevention and control, understaffing, overcrowding, and limited financial resources constitute real constraints to HCAI surveillance performance.

HCAI surveillance is a challenging task also because it requires a particular expertise after obtaining epidemiological data to assess the quality of the information produced, and to interpret its meaning and root cause in order to tailor intervention and prevention measures. The establishment and maintenance of surveillance encompasses various steps including specific components (Table 2.1).

Table 2.1
Main steps and components of a HCAI surveillance system

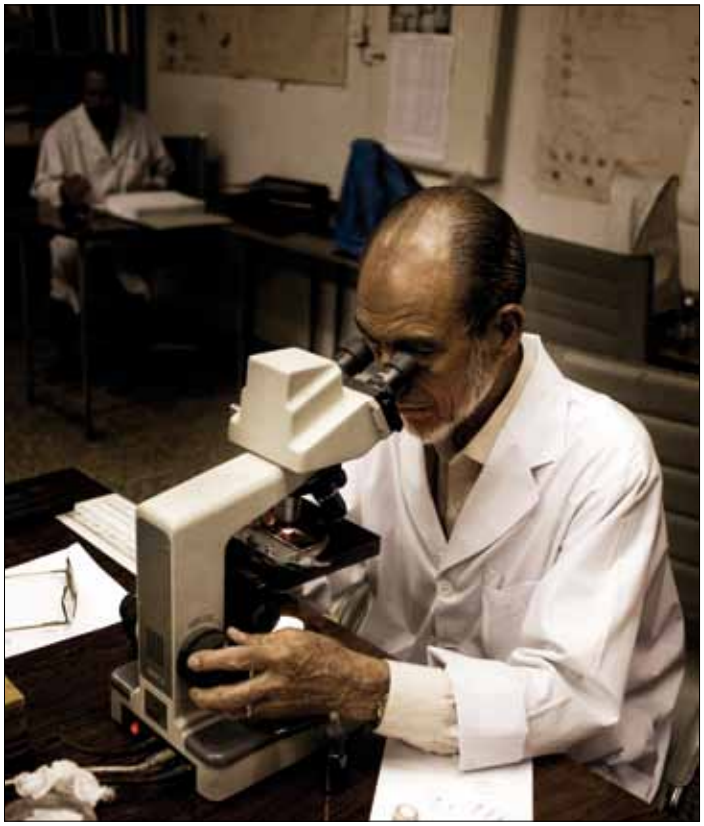
Surveillance steps	Components
1. Planning	• Assessment of available expertise, facilities and resources. • Identification of specific objectives, scope, and methods, according to the local reality. • Selection of standardized definitions and preparation of surveillance protocols.
2. Implementation	• Clinical data collection and other investigations conducted. • Completion and finalization of data collection forms. • Ongoing laboratory surveillance of sentinel microorganisms.
3. Analysis and feedback	• Data analysis and interpretation. • Local feedback adapted to the most appropriate means.
4. Interventions driven by surveillance	• Identification of appropriate and feasible interventions and priority areas according to specific results of surveillance. • Repetition of surveillance activities to assess the impact of interventions and their adjustment according to results.

Surveillance can be passive or active, prospective or retrospective. Passive surveillance is the most common form of surveillance and relies on data routinely generated from automated patient records, e.g. laboratory-based surveillance and data extraction from patient records after discharge. It has typically a low sensitivity and may lead to misclassification and underreporting because the criteria for diagnosis may be not easily available. However, passive surveillance is less demanding and may be the only feasible method in settings

lacking expertise and resources for active surveillance. Conversely, active surveillance should be conducted by trained personnel, usually infection control professionals, who look for evidence to meet standardized diagnostic criteria of HCAI by using a variety of data sources. Active surveillance has higher specificity and sensitivity than passive surveillance and should be preferred if resources permit.

Prospective surveillance monitors pre-selected indicators in hospitalized patients, according to a specific protocol. In some cases, it may be extended to the post-discharge period; this is particularly important for SSI.[29-38,44,45] Retrospective surveillance relies on previously-recorded routine data after patient discharge and, thus, relevant information may be lacking and some diagnostic criteria not fulfilled. Prospective surveillance is considered the gold standard for the collection of reliable and timely information, particularly in areas housing high-risk patients, and its inherent active nature strengthens the link to related interventions. However, it is more resource-expensive and time-consuming than retrospective surveillance.

The clinical history and diagnosis of a HCAI case is given below to illustrate its complexity, the diagnostic implications, and the consequences of this complication at all levels in a patient seeking care for different underlying diseases (A HCAI case: diagnosis and clinical situation).



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A HCAI case: diagnosis and clinical situation

In July 2009, a 46-year-old woman was admitted to a university hospital for further investigation of chronic eczema that had not responded to several treatment regimens with oral corticosteroids and topical medication.

On admission, the patient was found to be colonized with methicillin-resistant *Staphylococcus aureus* (MRSA) and received decolonization treatment with chlorhexidine and nasal mupirocin. A chest X-ray, performed because of persistent cough, revealed lung cancer. She was transferred to the oncology unit and surgical removal of the lesion was planned after three cycles of neoadjuvant chemotherapy. The first cycle was administered without any major complication. A port-a-catheter (PAC) was inserted via the jugular vein under antibiotic prophylaxis (cefuroxime). Swab cultures of the nose performed after de-colonization treatment remained positive for MRSA. The patient was discharged in good condition under treatment with oral dexamethasone and topical medication for her dermatitis, and with the PAC in place while waiting for her second chemotherapy cycle.

Ten days later, the patient was admitted to the emergency unit of a peripheral hospital for fever, severe hypotension, and leucocytosis. Pus secretions were observed on the PAC insertion site wound. Staphylococci were detected in secretions by microscopy and 24 hours later the blood cultures performed at admission grew MRSA. Intravenous antibiotic treatment with vancomycin was started and the patient was transferred to the university hospital where the catheter was removed and a drain was put in place. Culture of the catheter tip was performed and yielded MRSA.

A few days later, the patient developed neck oedema and septic thrombosis of the left internal jugular, subclavian, and axillary veins was diagnosed. Intravenous rifampin was added to the previous antibiotic therapy and a trans-oesophageal echocardiography was performed to exclude endocarditis. The examination proved negative. After three weeks of antibiotic therapy, the patient developed vaginal candidiasis that was treated with topical antifungal drugs.

The patient's condition slowly improved after an overall four-week intravenous antibiotic treatment course. Once recovered from the infection, the patient underwent her second chemotherapy cycle and was subsequently treated with radiotherapy and surgery.

Source: University of Geneva Hospitals, Geneva, Switzerland

Why is this a case of HCAI?

The patient was at risk because she probably developed immunosuppression due to long-term corticosteroid treatment. She was found to be colonized by MRSA and underwent standard topical eradication treatment, but she remained positive at first follow-up. She subsequently developed signs of infection following insertion of PAC: fever >38°C; inflammatory syndrome; and signs of a localized infection (purulent discharge of the catheter insertion site).

The following criteria indicated that the patient developed a deep surgical site infection associated with catheter-related bacteraemia:

- an infection occurring 30 days following a surgical procedure;
- purulent discharge at the PAC insertion site;
- deliberate opening of the PAC insertion site and PAC removal by the surgeon;
- positivity of the purulent secretions, blood cultures and catheter tip for the same microorganism (MRSA).

As a consequence of this complication:

- extensive vascular complications occurred (septic thrombosis of jugular, subclavian, and axillary veins);
- an invasive diagnostic procedure was performed to exclude endocarditis (trans-oesophageal echocardiography);
- an additional surgical intervention was required to remove the PAC;
- there was a need for long-term antibiotic treatment;
- multiple peripheral venous lines and one central venous line were inserted for supportive and antibiotic therapy;
- vaginal mycosis occurred due to prolonged antibiotic therapy;
- there was a delay in the treatment of the pulmonary cancer;
- the patient (mother of three children) was hospitalized and away from home for 35 days.

3.

The burden of endemic health care-associated infection in high-income countries

National HCAI surveillance systems exist in several high-income countries and data are usually available through national reports and/or nationwide, or multicentre studies published in the scientific literature (Figure 3.1). According to our review, 131 national or multicentre studies conducted in 23 high-income countries were published from 1995 to 2010. The European Centre for Disease Prevention and Control (ECDC) reported that 13/28 (46.4%) European high-income countries had national surveillance systems in place in 2008 to monitor either ICU-acquired infections, SSI, or both, and were regularly reporting to the Hospitals in Europe Link for Infection Control through Surveillance (HELICS) network.[46] In the USA, more than 3000 health-care facilities regularly report data on ICU-acquired infections to the NHSN (http://www.cdc.gov/nhsn/), established by the Centers for Disease Control and Prevention (CDC). Other high-income countries, such as Australia, France, Germany, and Japan, have coordinated surveillance at national or state level. Our literature review on high-income countries identified 55 studies with a national scope, mostly conducted in countries with a national surveillance system in place.

In national and multicentre studies identified, the prevalence of hospitalized patients who acquired at least one HCAI ranged from 3.5%[47] to 12%[48] (Figure 3.2). Pooled HCAI prevalence obtained through meta-analysis from studies conducted in mixed patient populations was 7.6 episodes per 100 patients (95% CI 6.9-8.5) and 7.1 affected patients per 100 patients (95% CI 6.5-7.8).[14-18,47-75] HCAI prevalence figures reported in the most recent studies available from high-income countries are shown in Figure 3.3.

Figure 3.1

Number of national and multicentre studies reporting health care-associated infection in high-income coutries, 1995-2010

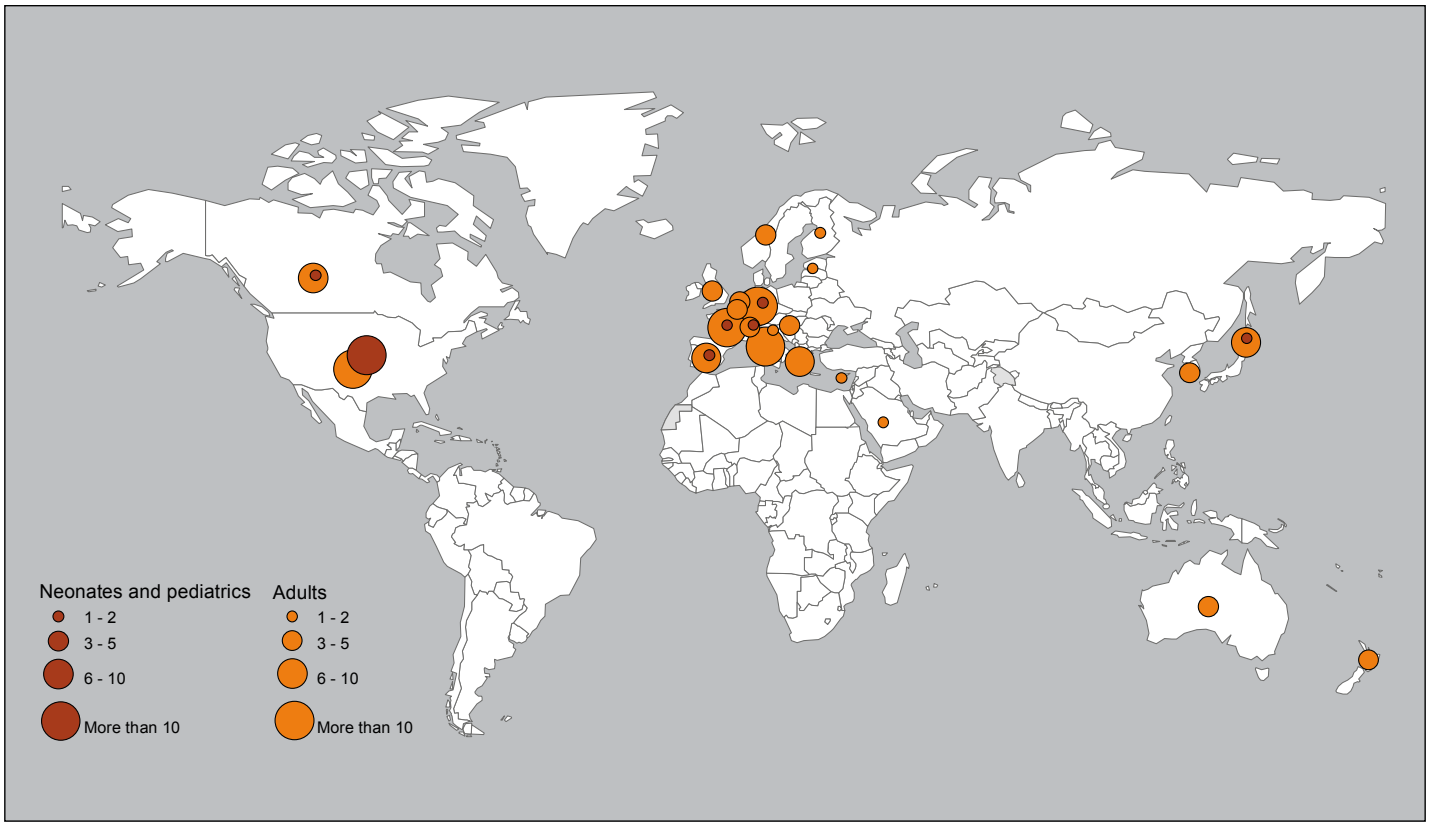


Figure 3.2

Health care-associated infection prevalence in high-income countries versus low- and middle-income countries, 1995-2010

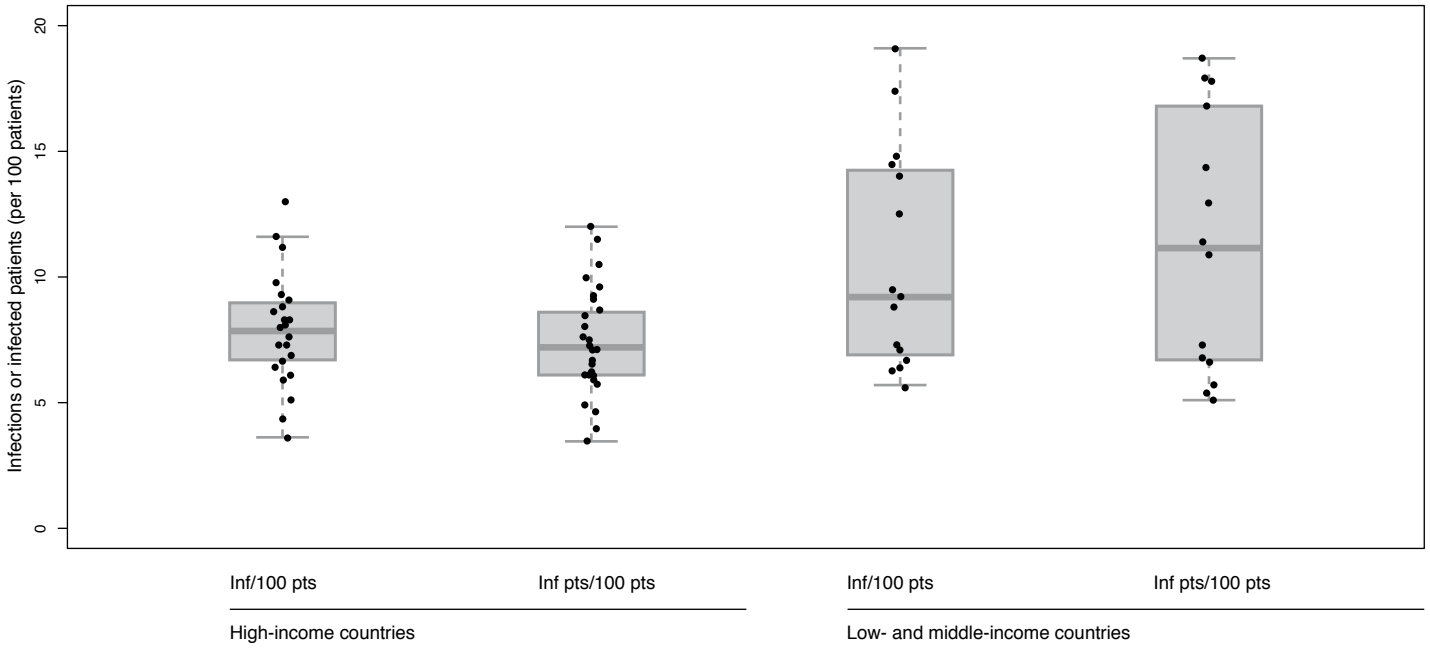
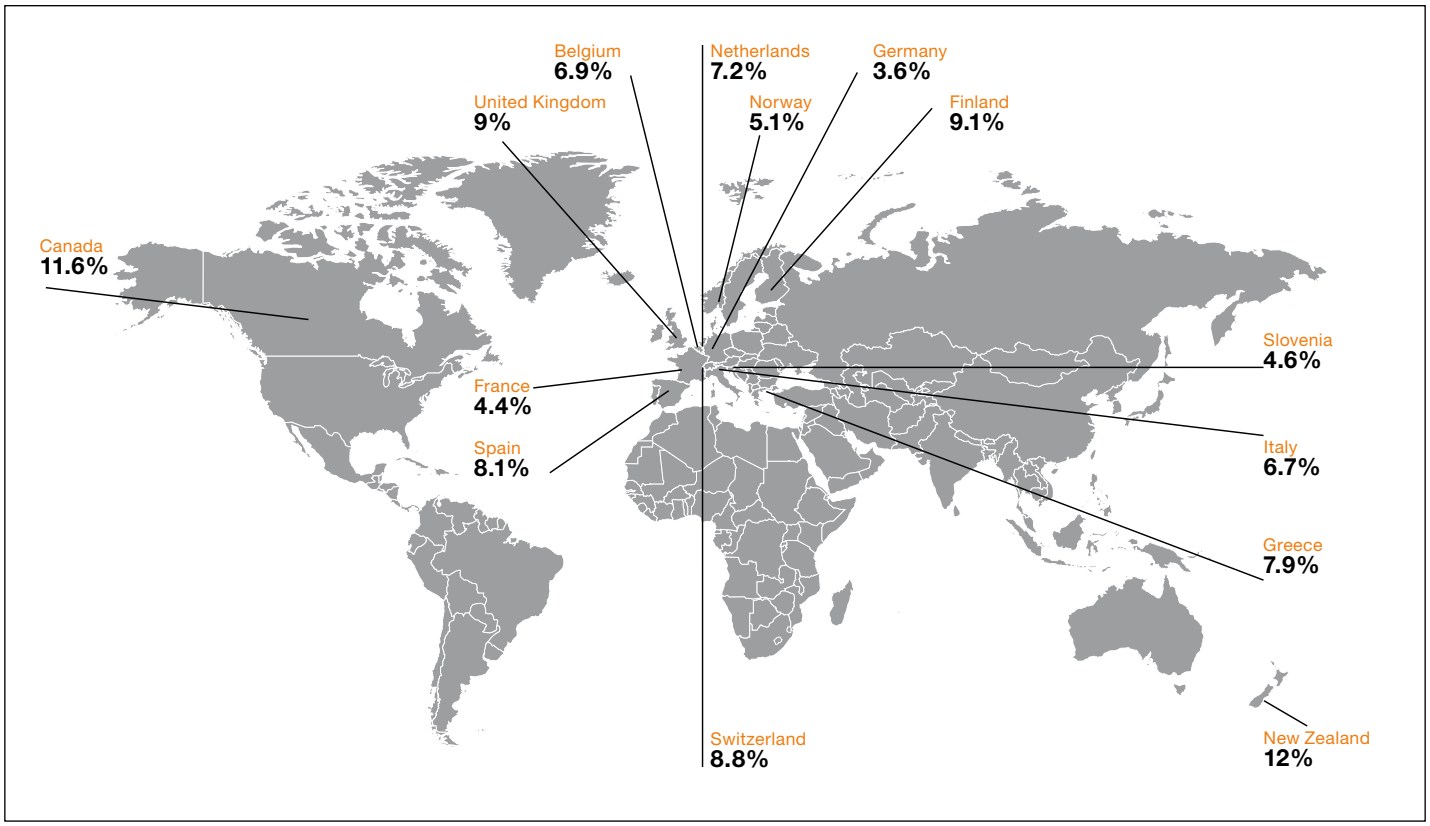


Figure 3.3

Prevalence of health care-associated infection in high-income coutries, 1995-2010*



* For countries with more than one study, the most recent figures are included.

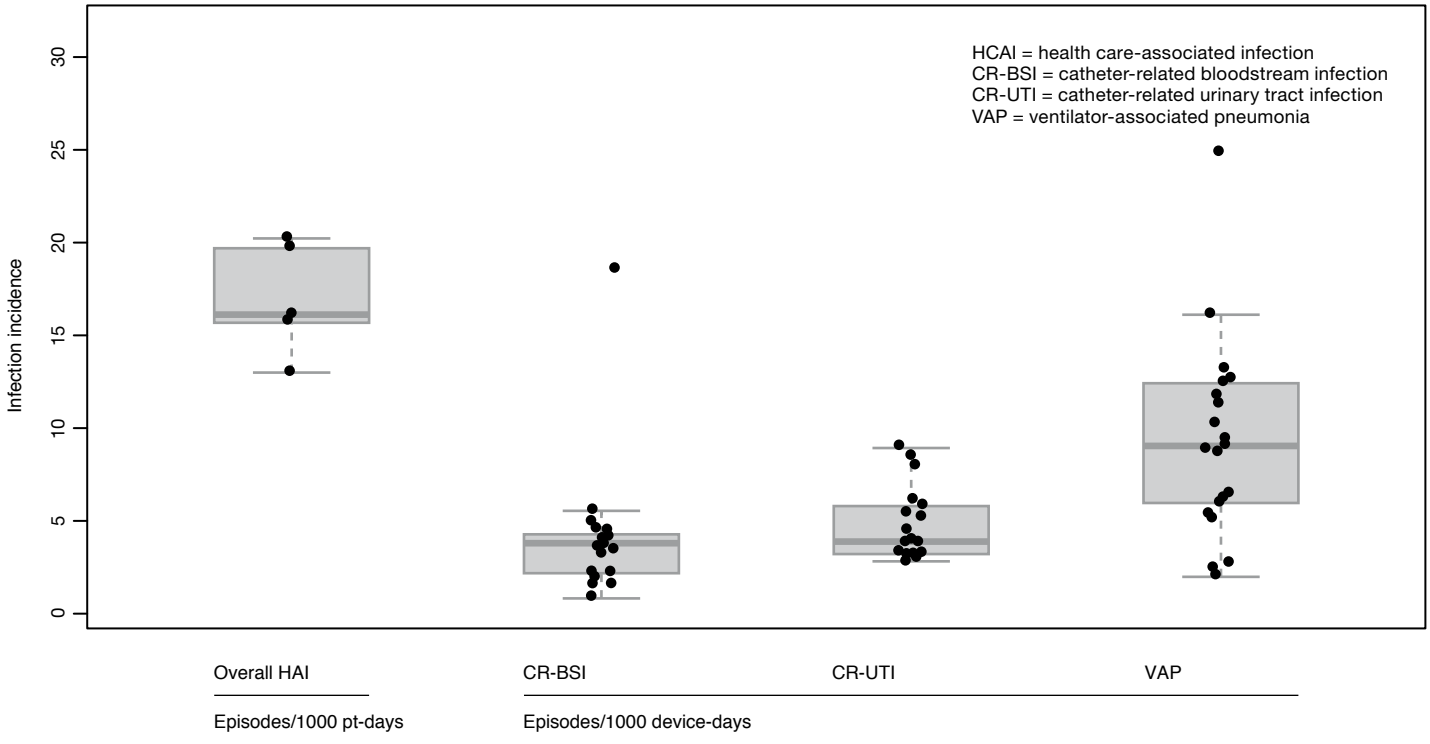
The ECDC reported that approximately 4 131 000 patients are affected by about 4 544 100 episodes of HCAI every year in Europe, with a mean HCAI prevalence of 7.1%.[76] The estimated HCAI incidence rate in the USA was 4.5% in 2002, corresponding to 9.3 infections per 1000 patient-days and 1.7 million affected patients.[77] In the USA and Europe, UTI was the most frequent type of infection hospital-wide (36% and 27%, respectively).[76,77] In the USA, this was followed by SSI (20%), bloodstream infection (BSI), and pneumonia (both 11%).[77] In Europe, the second most frequent type was lower respiratory tract infection (24%), followed by SSI (17%), and BSI (10.5%).[76] According to several studies, the frequency of SSI varies between 1.2% and 5.2% in high-income countries.[43,44,77-88]

- 13/28 (46.4%) European high-income countries reporting either ICU-acquired infections, SSI, or both, to the HELICS network in 2008.
- HCAI pooled prevalence in mixed patient populations in high-income countries: 7.6%.
- More than 4 million patients affected by HCAI every year in Europe; 1.7 million affected patients in USA.
- Frequency of SSI varies between 1.5% and 5.2% in high-income countries.
- In high-income countries, approximately 30% of ICU patients are affected by at least one episode of HCAI.

The HCAI burden is much more severe in high-risk populations, such as patients admitted to ICUs, burn and transplant patients, and neonates. According to a recent European multicentre study, the proportion of infected patients in the ICU can be as high as 51%; most of these are health care-associated.[89] In high-income countries, approximately 30% of ICU patients are affected by at least one episode of HCAI with substantial associated morbidity and mortality.[90] Based on large studies from USA and Europe included in our review, HCAI incidence density ranged from 13.0 to 20.3 episodes per 1000 patient-days (Figure 3.4) and pooled cumulative incidence was 17.0 episodes per 1000 patient-days in adult high-risk patients in industrialized countries (Table 3.1 and Figure 3.4).[77,91-94] High frequency of infection is associated with the use of invasive devices, in particular central lines, urinary catheters, and ventilators. In a report from the USA NNIS system, 83% of episodes of hospital-acquired pneumonia were associated with mechanical ventilation, 97% of UTIs occurred in catheterized patients, and 87% of primary BSI in patients with a central line.[93] Among adult ICU patients in high-income countries, pooled cumulative incidence densities of catheter-related BSI (CR-BSI), urinary catheter-related UTI (CR-UTI), and ventilator-associated pneumonia (VAP) were 3.5 (95% CI 2.8-4.1) per 1000 CL-days,[95-110] 4.1 (95% CI 3.7-4.6) per 1000 urinary catheter-days,[98-110] and 7.9 (95% CI 5.7-10.1) per 1000 ventilator-days,[98-111] respectively (Table 3.1 and Figure 3.4). Comparisons with data available from the NHSN system[109] and the German hospital infection surveillance system (Krankenhaus Infektions Surveillance System [KISS])[112]

Figure 3.4

Incidence of overall health care-associated infection and device-associated infection in high-risk adult patients in high-income countries, 1995-2010



highlight that these pooled values are similar, although slightly higher. On average, VAP is the most frequent type of infection in the ICU (32%), followed by CR-UTI and CR-BSI (both 20%), according to studies included in our review.[91-96,98-111,113-118]

Very low birth weight (<1500g) neonates requiring intensive care are a population at high risk for HCAI. Data from recent multicentre studies conducted in Canada and Germany reported that 23.5% and 12.3% of patients are affected, respectively.[119,120] Lower HCAI rates are reported in paediatric ICUs. For instance, in the USA, HCAI incidence in this patient population was reported to be 5.7%.[121] Device-associated infection densities were 1.8 episodes per 1000 ventilator-days, 3 episodes per 1000 CL-days, and 4.2 episodes per 1000 urinary catheter-days, for VAP, CR-BSI, and CR-UTI, respectively.[109]

In large studies conducted in France, Germany, and Italy included in our review, of 13 954 isolates, the most frequently reported pathogens in ICU-acquired infections were: *Staphylococcus aureus* (21.8%); enterobacteriaceae (20.2%); *Pseudomonas* spp. (17.2%); enterococci (10.0%); *Escherichia coli* (9.1%); *Candida* spp (8.8%); coagulase-negative staphylococci (7.0%); and *Acinetobacter* spp (5.1%).[92,115,122,123] These microbiological patterns were similar to those reported in 1995 by the European Prevalence of Infection in Intensive Care (EPIC) study,[124] apart from coagulase-negative staphylococci, which were more commonly observed. Among 42 247 isolates from different studies included in our review,[16-18,48,51,56,57,62,65,66,71,125] *E. coli* (20.1%) and *S. aureus* (17.8%) were the most frequent single pathogens causing HCAI in mixed patient populations, thus reflecting the fact that UTI and SSI are the most common types of infection encountered. Other key pathogens were: *Pseudomonas* spp. (11.5%), enterobacteriaceae (10.6%); *Candida* spp. (6.7%); enterococci (6.5%); *Acinetobacter* spp. (5.8%); and coagulase-negative staphylococci (5.3%).

Table 3.1

Pooled cumulative incidence density of HCAI and device-associated infection in adult ICU patients in high-, middle- and low-income countries.

Surveillance networks/reviews, study period, country	HCAI/ 1000 patient-days (95% CI)	Patient days	CR-BSI/ 1000 central line days (95% CI)	Catheter-days	CR-UTI/ 1000 urinary catheter days (95% CI)	Urinary catheter-days	VAP/ 1000 ventilator days (95% CI)	Ventilator-days
NHSN, 2006–2008, USA#[109]	/	/	2.1	699 300	3.4	546 824	2.9	383 068
KISS, 2004-2009, Germany[112]	/	/	1.3	4 002 108	2.0	4 757 133	5.1	2 391 381
Systematic review, high-income countries 1995-2010*	17.0 (14.2-19.8)	32 537 324	3.5 (2.8-4.1)	5 339 322	4.1 (3.7-4.6)	13 614 567	7.9 (5.7-10.1)	5 339 322
INICC, 2003–2008, 25 developing countries†[158]	/	/	7.4	362 882	6.1	403 545	14.7	275 111
Systematic review, low- and middle-income countries (1995-2010)*	42.7 (34.8-50.5)	193 139	12.2 (10.5-13.9)	891 220	8.8 (7.4-10.3)	970 710	23.9 (20.7-27.1)	679 950

HCAI = health care-associated infection; CR-BSI = catheter-related bloodstream infection; CR-UTI = catheter-related urinary tract infection; VAP = ventilator-associated pneumonia; NHSN = National Healthcare Safety Network; KISS=Krankenhaus Infektions Surveillance System; INICC=International Nosocomial Infection Control Consortium.

\# Medical/surgical ICUs in major teaching hospitals
* Specific references can be found in the text
† Argentina, Brazil, China, Colombia, Costa Rica, Cuba, Greece, India, Jordan, Kosovo, Lebanon, Lithuania, Macedonia, Mexico, Morocco, Pakistan, Panama, Peru, Philippines, Salvador, Thailand, Tunisia, Turkey, Venezuela, Vietnam

4.

The burden of endemic health care-associated infection in low- and middle-income countries

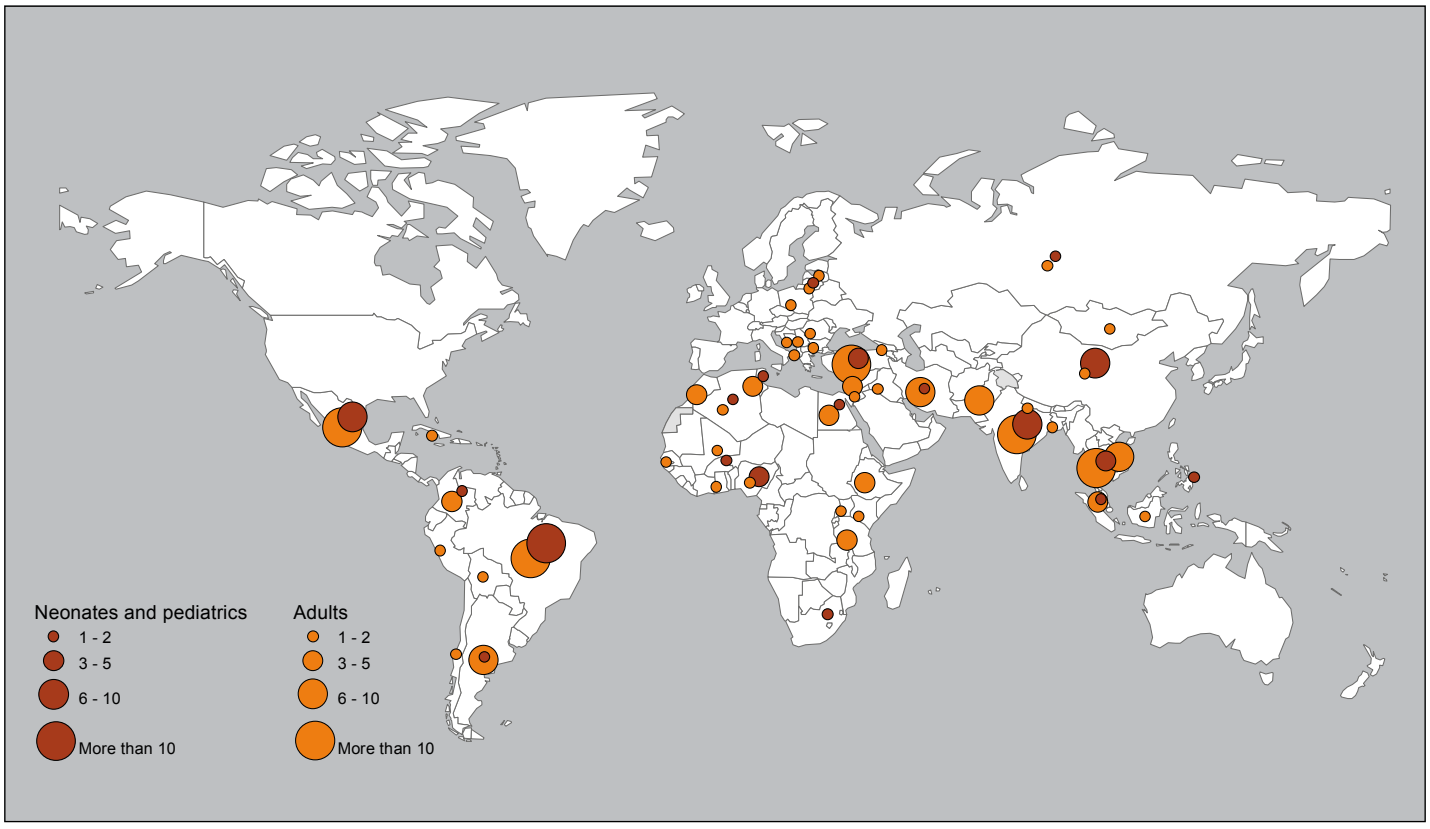
While HCAI surveillance systems are in place at national/sub-national level in many developed countries, only 23 developing countries (23/147 [15.6%]) reported a functioning national surveillance system, according to a survey conducted by the WHO First Global Patient Safety Challenge (*Clean Care is Safer Care*; http://www.who.int/gpsc/en/) in 2010. As highlighted in section 2, HCAI surveillance is a highly demanding and challenging task and settings with limited resources experience many constraints to evaluate the burden of HCAI. In low- and middle-income countries, regular monitoring of HCAI occurrence may be unfeasible at national level and, thus, Ministries of Health are unable to report information on the burden of HCAI. In addition, a limited number of studies in these settings have been published in the scientific literature.

The *Clean Care is Safer Care* team of WHO Patient Safety, in collaboration with the University of Geneva Hospitals, recently published a systematic review and meta-analysis on the endemic burden of HCAI in developing countries.[3] Data included in this report represent an update of this work. In our review, covering the period from 1995 to 2010 (Box 1), 276 papers included relevant information on the epidemiology of the four most frequent types of HCAI (SSI, UTI, BSI, health-care associated pneumonia [HAP]/VAP) in low- and middle-income countries. Only 46% (126/276) met the criteria usually defining high-quality epidemiological studies (Box 1).

A review of countries where studies were performed and regional coverage revealed clearly an extremely fragmented picture of the endemic burden of HCAI in the developing world, with very scanty

Figure 4.1

Number of studies* reporting health care-associated infection in low- and middle-income coutries, 1995-2010



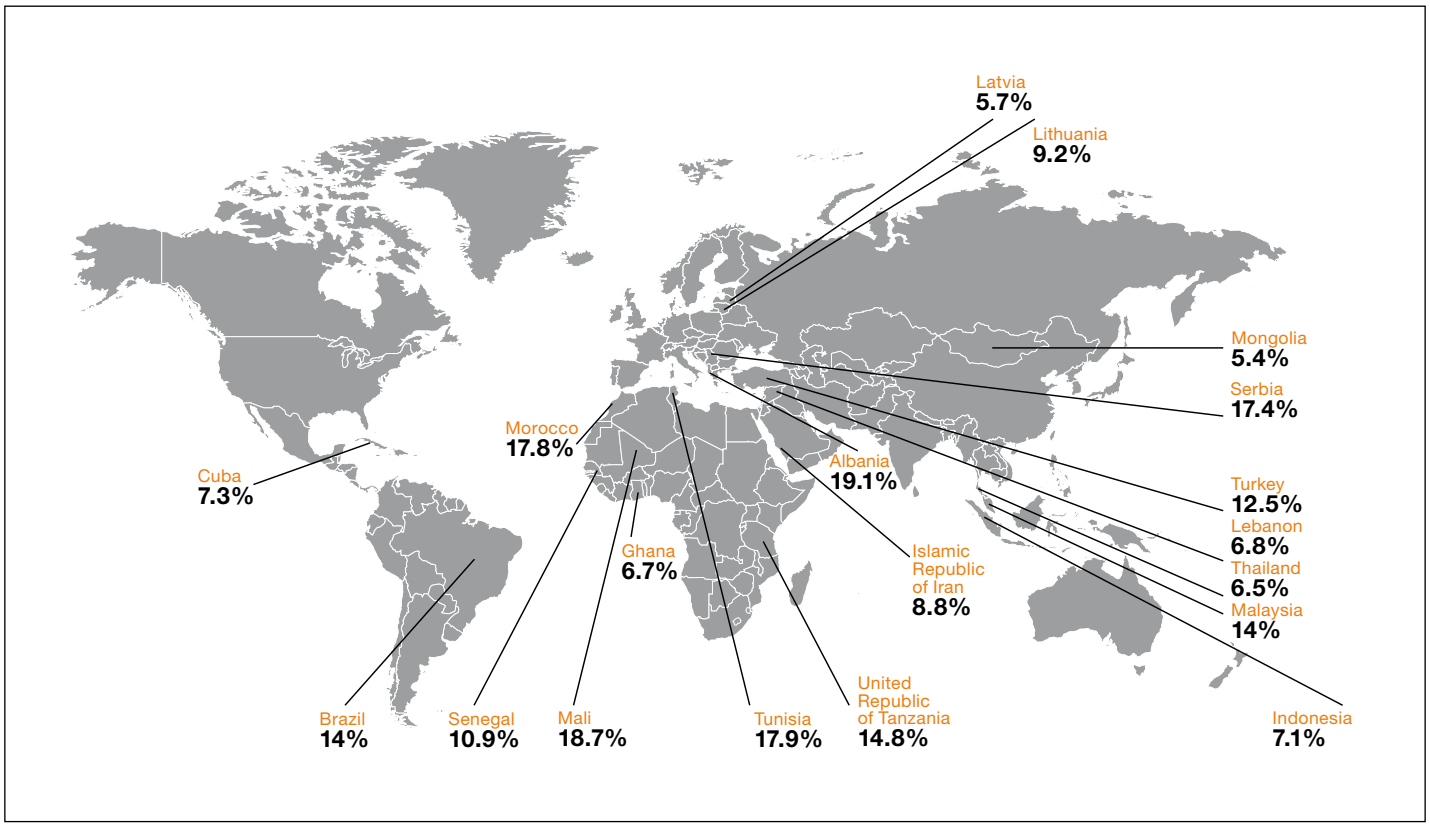
* Studies with any scope (i.e. conducted at the unit, facility, multicenter, or national level) are included.

information available from some regions (particularly Africa and the Western Pacific) (Figure 4.1). However, even in regions where overall more studies were conducted and published (Europe and the Americas), several countries are covered by several reports, whereas others are not represented by any published surveillance study (Figure 4.1). Brazil, India, Mexico, Thailand, and Turkey were identified as the countries with the highest number of studies. Only nine studies from four countries (Cuba, Mexico, Thailand, and Turkey) were conducted at national level.[20,25,126-132] An additional 39 multicentre studies were reported from different countries, either conducted in multiple hospitals in one city or in a country territory.[38,133-169] According to our review, 66% (97/147) of developing countries have no published data at all. The limited number of studies with a broad scope, together with the lack of national surveillance systems, significantly hamper any attempts to estimate the burden of HCAI at country or regional level in low- and middle-income countries. Studies from single hospitals cannot be considered representative of the endemic epidemiology of HCAI in a country. In particular, most studies were conducted in teaching/university hospitals (144/276 [52.2%]), which represent a specific type of context and not the broad range of health-care settings in place in countries. Most importantly, the HCAI surveillance programme of the International Nosocomial Infection Control Consortium (INICC) (http://www.inicc.org/) is of great assistance to help bridge some of the gaps and to gauge the extent of the problem. This fast-growing network coordinates data collection on device-associated infections in several low- and middle-income countries and has published already four international studies[158,170-173] and many reports from individual countries or facilities.[137,139,144,147,174,175]

Many studies conducted in health-care settings with limited resources reported HCAI rates higher than in developed countries. Hospital-wide prevalence of HCAI varied from 5.7% to 19.1% (Figures 3.2 and 4.2) with a pooled prevalence of 10.1 per 100 patients (95% CI 8.4-12.2) and most studies reported proportions of infected patients higher than 10%; the pooled prevalence of affected patients was 10.2 per 100 patients (95% CI 9.0-13.0).[25,27,126,128-130,149,157,164,166,167,169,176-188] Of note, it was calculated that the pooled HCAI prevalence was significantly higher in high- than in low-quality studies (15.5% vs 8.5%, respectively).[3] Similarly, the proportion of infected patients was higher in high-quality studies (13.5% vs 7.2%).[3] The most frequent type of infection in these mixed patient populations was SSI (29.1%), followed by UTI (23.9%), BSI (19.1%), HAP (14.8%), and other infections (13.1%).[3]

Figure 4.2

Prevalence of health care-associated infection in low- and middle-income coutries, 1995-2010



- Only 23 developing countries (23/147 [15.6%]) reported a functioning HCAI national surveillance system in 2010.
- No published data on HCAI endemic burden from 66% (97/147) of developing countries, according to the current review.
- HCAI pooled prevalence in mixed patient populations in low- and middle-income countries: 10.1%. In high-quality papers, prevalence: 15.5%.
- SSI is the most frequent HCAI hospital-wide in low- and middle-income countries with a pooled incidence of 11.8 per 100 patients undergoing surgical procedures.
- In low- and middle-income countries, incidence of ICU-acquired infection is at least 2–3 fold higher than in high-income countries; device-associated infection densities up to 13 times higher than in the USA were reported in some studies.

The increased burden of HCAI in low- and middle-income countries affects especially high-risk populations, such as patients admitted to ICUs and newborns, with HCAI frequency several-fold higher than in industrialized countries, particularly for device-associated infections. The proportion of patients with ICU-acquired infection was as high as 35.2% (95% CI 24.2-48.0) (pooled cumulative incidence). The incidence of HCAI ranged from 4.4% up to 88.9%.[28,137,139,144,147,175,189-195] HCAI incidence density in settings with limited resources significantly varied between 4.1 and 91.7 episodes per 1000 patient-days (Figure 4.3), and pooled cumulative incidence was 42.7 episodes per 1000 patient-days (95% CI 34.8-50.5) (Table 3.1).[28,135,137,139,144,147,175,189,190,192-196] The latter was significantly higher than reported in the USA (13 per 1000 patient-days)[77] and in the results of our meta-analysis related to high-income countries (17.0 per 1000 patient-days). Data reported in several studies from Argentina and Turkey indicated that infection density in ICU patients can be higher than 50 per 1000 patient-days.[28,135,193,194] Pooled cumulative incidence densities of CR-BSI, CR-UTI, and VAP among adult ICU patients in low- and middle-income countries were 12.2 per 1000 CL-days (95% CI 10.5-13.9),[134-136,138-141,144,147,158,161,162,170,171,175,197-200] 8.8 per 1000 urinary catheter-days (95% CI 7.3-10.4),[134-141,144,147,158,161,170,171,197,198,201] and 23.9 per 1000 ventilator-days (95% CI 20.7-27.1),[134-141,144,147,158,161,170,171,175,197,198,202-204] respectively (Table 3.1 and Figure 4.3). These values are higher than those most recently reported by the INICC[158] in a network of ICUs in developing countries and are two- to three-fold higher than in ICUs in high-income countries (Table 3.1 and Figure 3.4). An analysis of individual studies revealed that device-associated infection densities up to 13 times higher than in the USA can be detected.[3] Considering that these types of infections are a clear reflection of the safety level of invasive procedures, it is evident that patients in developing countries are at greater risk of being infected through these devices.

A limited number of studies are available on HCAI epidemiology in the paediatric population. According to a systematic review by Zaidi and colleagues,[205] neonatal infection rates in developing countries are three to 20 times higher than in industrialized countries. Among hospital-born babies, these infections are responsible for 4% to 56% of all causes of death in the neonatal period, with three-quarters occurring in the South-East Asia Region and sub-Saharan Africa.

HCAI rates are particularly high in neonatal and paediatric ICUs. Data pooled from four comparable studies conducted in Brazilian neonatal ICUs revealed an overall cumulative incidence as high as 40.8 infections per 100 patients (95% CI 16.1-71.1), and a HCAI incidence density of 30.0 episodes per 1000 patient-days (95% CI 25.0-35.0).[3] In studies in neonatal and paediatric ICUs retrieved through our review and as reported also by Zaidi and colleagues, VAP and CR-BSI densities were particularly high, ranging from 10.9 to 143 episodes per 1000 ventilator-days and from 2.1 to 60.0 episodes per 1000 catheter-days, respectively.[206-216]

Almost half of studies focusing on specific types of infection were related to SSI (62/131),[36-38,131,150-156,217-244] probably because it can be identified more easily according to clinical criteria. SSI appears to be also the most frequent HCAI hospital-wide in low- and middle-income countries and more than 10% of operated patients usually develop SSI. Reported SSI cumulative incidence ranged from 0.4 to 30.9 per 100 patients undergoing surgical procedures and from 1.2 to 23.6 per 100 surgical procedures.[3] SSI pooled rates were 11.8 per 100 patients undergoing surgical procedures (95% CI 8.6-16.0) and 5.6 per 100 surgical procedures (95% CI 2.9-10.5).[3] This level of risk for patients undergoing surgical procedures is significantly higher than in developed countries. For example, SSI incidence reached 30.2% in the surgical unit of a university hospital in Brazil.[32] Similarly, 30.9% of paediatric patients acquired an infection following surgery in a teaching hospital in Nigeria.[245]

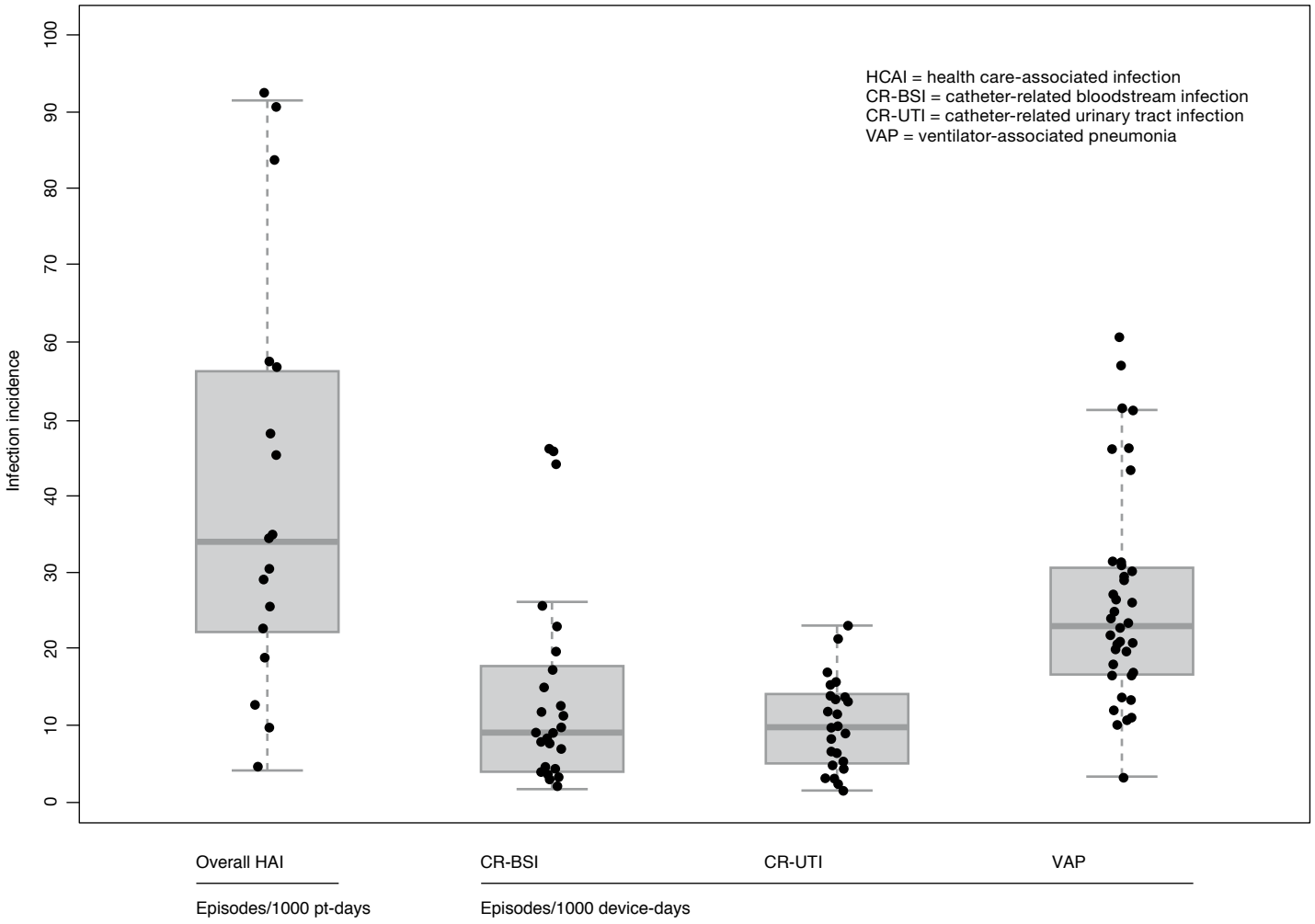
A recently-published review of microbiological patterns of HCAI from 28 studies conducted in developing countries[3] reported gram-negative rods as the most common nosocomial isolates, both in mixed patient populations and in high-risk patients. The most frequent single pathogens were *S. aureus* in mixed patient populations, and *Acinetobacter* spp. in high-risk patients. The latter was the second most frequent pathogen identified for VAP (24.0%) and, unexpectedly, for BSI (17.7%). *S. aureus* was the most frequent cause of both SSI and BSI. Surprisingly, gram-negative rods were isolated in a large proportion of SSIs. A limited number of studies reported data on antimicrobial resistance patterns. Only information on methicillin resistance of *S. aureus* compiled from eight studies was provided and showed that as many as 54.5% of all isolates (158/290) carried this pattern.

Zaidi and colleagues[205] previously reported alarming estimates among neonates indicating that 51% of *Klebsiella* spp. were extended-spectrum beta-lactamase-producers, and 38% and 64% of *S. aureus* were resistant to methicillin and co-trimoxazole, respectively. The authors found also that 70% of pathogens isolated in endemic BSI may be resistant to ampicillin and gentamicin, the

antimicrobials recommended by WHO for the empiric therapy of neonatal sepsis. The dramatic paucity of data on antimicrobial resistance of health care-associated pathogens in developing countries was also highlighted by Okeke and colleagues in a comprehensive review on this topic.[246]

Figure 4.3

Incidence of overall health care-associated infection and device-associated infection in high-risk patients in low- and middle-income countries, 1995-2010



5.

The impact of health care-associated infection worldwide

The burden of HCAI worldwide needs to be highlighted not only because of the large number of patients affected every year, but also for its significant impact in terms of excess costs, prolonged hospital stay, attributable mortality, and other complications. Data on these important indicators are difficult to retrieve as they require complex evaluation, particularly to confirm that they are directly linked to HCAI episodes and not to other factors. Methods of recording and filing patient clinical data vary worldwide, with a limited availability of electronic-based systems in developing countries. Health-care financial systems also differ with a broad range of payer sources (e.g. a governmental agency, private insurance company, or even the patients themselves) and local charges, thus leading to complex estimates and calculations of costs and potentially limiting inter-hospital and international comparisons.

Similar to many other adverse events experienced by patients while seeking health care, HCAIs lead to added suffering and the psychological and financial burden to patients. Given that HCAI is inherently linked to health-care workers' behaviour (e.g. sub-optimal hand hygiene practices) and, in some cases, to health-care system gaps (e.g. lack of adequate equipment), this burden translates into a profound frustration and loss of trust in the system and health-care professionals. The case of a 13-year-old patient illustrates the incredible long-term suffering, pain. and fear that one HCAI can cause (Patient case story).

Core evidence available from high-income countries

Overall estimates of HCAI impact are available for some high-income countries and help understand the magnitude of its consequences. European estimates indicate that HCAIs cause 16 million extra-days of hospital stay and 37 000 attributable deaths annually, but also contribute to an additional 110 000 deaths.[76]

The burden of HCAI is also reflected in significant financial losses. According to a report from the ECDC, these infections account for approximately € 7 billion per year, including direct costs only.[76] Recent national estimates from Belgium showed that about 900 000 bed-days are complicated every year by at least one episode of HCAI.[52] Similar dramatic figures were reported in the USA and around 99 000 deaths were attributed to HCAI in 2002.[77] Of these, approximately 36 000 were due to pneumonia, 31 000 to BSI, 13 000 to UTI, 8 200 to SSI, and 11 062 to other infections. The annual economic impact of HCAI in the USA was approximately US$ 6.5 billion in 2004.[77]

Patient case story

My name is Raihama and I am 13 years old. Last year, I was admitted to hospital on 16 July for a gallstone problem and two days later I was operated. It was only three months after the operation that I was finally discharged from the hospital, because I picked up a nosocomial infection. Fortunately, I had a good friend who brought me school work every week and taught me what she had learned in school. She also wrote down all the words and calculations of the homework for me, because the infection had settled in my arm. I have never been able to move my arm as I did before. I can no longer do all I want to do with this arm.

I am Raihama's mother. She developed an infection after her operation and we had a lot of difficulties over those three months. We had to go to several hospitals. In the first hospital, they never accepted that Raihama's infection was due to her operation and nobody helped us take care of her situation. We had to look for good physicians and paid for all the expenses ourselves. The infection has left irreversible damage on her arm because it spread to the bones. We were told that it was an osteomyelitis.

For three months, I had to leave my two little kids early every morning to go to a hospital far from our home to take care of Raihama and I only got home late in the evening. The kids didn't see me any more and they were very worried for the health of their sister. Nobody was feeling good at home. Now every time Raihama tells me that she has a headache or she doesn't feel well, my heart starts beating fast and I get really worried. I am scared that everything is starting again.

Source: WHO Patients for Patient Safety (http://www.who.int/patientsafety/patients_for_patient/en/)

In studies mainly conducted in high-income countries, crude mortality rates associated with HCAI vary from 12% to 80%, depending on the patient population.[90] As mentioned previously, estimating the excess mortality due to HCAI is challenging, especially in high-risk patients who are at greater risk of death because of severe underlying diseases. For example, Soufir and colleagues[247] reported that crude mortality rates were significantly higher in critically-ill patients affected by CR-BSI compared to those non-affected (50% vs 21%, respectively). When adjusting for admission prognostic factors, infection remained associated with mortality, but not after taking into account severity scores before infection onset. Several additional studies brought controversial results, some corroborating the hypothesis that HCAI patients are at higher risk of death. Among these, a prevalence study conducted in 17 Western European countries showed that clinical sepsis, pneumonia, and BSI were all independently associated with an increased risk of death in critically-ill patients.[248]

Of note, according to studies conducted in high-income countries, some infections, such as VAP and BSI, have a more severe impact than others. VAP attributable mortality has been estimated at between 7% and 30% and attributable costs at US$ 10 000–25 000 per case.[249,250] Of approximately 250 000 CR-BSI occurring every year hospital-wide in the USA, about 28 000 lead to deaths in ICU patients, with an annual cost of up to US$ 2.3 billion.[251] Furthermore, in a recent study performed in four European countries, additional length of stay per CR-BSI episode varied between 4 and 14 days. Additional associated costs per episode ranged from € 4 200 to € 13 030, representing annual costs to health-care systems of between € 53.9 million in the United Kingdom and € 130 million in France.[252]

- In Europe, HCAIs cause 16 million extra-days of hospital stay and 37 000 attributable deaths (and contribute to an additional 110 000). Associated costs: approximately € 7 billion annually.
- In the USA, around 99 000 deaths were attributed to HCAI in 2002. Associated costs: approximately US$ 6.5 billion in 2004.
- VAP attributable mortality: between 7% and 30%; VAP attributable costs: US$ 10 000–25 000 per case.
- CR-BSI additional length of stay: 4–14 days. Additional associated costs per episode in European countries: € 4 200–13 030.

Core evidence available from low- and middle-income countries

Very limited data are available at the national level to assess the impact of HCAI in low- and middle-income countries. Conversely, an increasing body of information has been published at the institutional level. We identified 89 studies reporting data on the burden of HCAI in terms of mortality, costs and increased length of stay in health-care settings.[20,22,24-28,126,133,135,138,139,142-146,148, 158,160,164,170,175, 177,180,189,190,193,195,206,208,210,211,214-216,218,224,226,227,230,232,233,235,237,238,239,253-292]

However, in most cases, only crude mortality rates in patients affected by HCAI were reported, without taking into account other risk factors or major confounders, or by comparing these with non-infected patients. Thus, no conclusions can be drawn on the risk of death actually attributable to HCAI. Several studies reported significantly higher mortality in infected patients, in particular in paediatric and adult ICUs.[133,135,139,194,211,216,261,269,273,277] According to the 2003-2008 INICC report related to 173 ICUs in Latin America, Asia, Africa, and Europe, crude excess mortality in adult patients was 18.5%, 23.6% and 29.3%, for CR-UTI, CR-BSI and VAP, respectively.[158] Increased length of stay associated with HCAI varied between 5 and 29.5 days.[22,24,126,133,135,139,143,160,175,189,193,194,206,210,211,214-216,218,230,237-239,253,257,260,265,267,274,282,283,289,290,292,293]

In a multicentre study conducted in ICUs in India, excess length of stay and mortality due to VAP, CR-UTI, and CR-BSI were 11, 8 and 5 days, and 19.0%, 11.6%, and 4.0%, respectively.[139] In an Argentinean ICU, the attributable mortality from VAP, CR-UTI, and CR-BSI was 35.0%, 25.0%, and 5.0%, respectively.[135] Wide variations in cost estimates associated with HCAI were observed between countries. The economic impact in Belo Horizonte, Brazil, was estimated to be equal to US$ 18 million in 1992, based on costing information from the USA and Costa Rica.[164] In an 800-bed, tertiary care, university hospital in Malaysia with a HCAI prevalence of 13.9 per 100 patients, the cost of antibiotics prescribed to treat HCAI was estimated at US$ 521 000 per year.[180] Costs associated with hospital-acquired BSI in cardiac surgical patients in a hospital in India averaged US$ 22 873 and represented an excess cost of US$ 14 818 per case compared with non-infected patients.[273] In Mexican ICUs, the overall average cost of a HCAI episode was US$ 12 155 with an excess cost of US$ 11 591 per case of CR-BSI.[143,279] In several ICUs in Argentina, the overall extra-cost estimates for CR-BSI and HAP averaged US$ 4888 and US$ 2255 per case, respectively.[133,294]

- Increased length of stay associated with HCAI in developing countries: 5-29.5 days.
- Excess mortality due to HCAI in adult patients in Latin America, Asia, Africa: 18.5%, 23.6%, and 29.3%, for CR-UTI, CR-BSI, and VAP, respectively.
- Economic impact of HCAI in Belo Horizonte, Brazil, in 1992: US$ 18 million.
- In Mexican ICUs, overall average cost of a HCAI episode: US$ 12 155.
- In ICUs in Argentina, overall extra-costs for CR-BSI and HAP: US$ 4 888 and US$ 2 255 per case, respectively.

6.

Lessons learned and the way forward

By mapping and scrutinizing the studies in the scientific literature, a global picture of the endemic burden of HCAI can be captured for the first time with compiled data from many countries and, importantly, an assessment of differences between high-, low- and middle-income countries. The key finding is that the burden of HCAI worldwide is very high in terms of morbidity, mortality, extra-costs, and other outcome indicators. This is particularly true for developing countries where awareness of the problem remains extremely limited, and because other health priorities take precedence over patient safety considerations.

Of every 100 hospitalized patients at any given time, 7 and 10 of them will acquire a HCAI in developed and developing countries, respectively. According to high-quality studies, this proportion increases to 15 per 100 patients in developing countries.[3] HCAI is more frequent in critically-ill patients admitted to ICUs. In this patient population, the increased risk in settings with limited resources is particularly disturbing with an overall frequency of infection as high as 42.7 episodes per 1000 patient-days in developing countries vs 17.0 episodes per 1000 patient-days in industrialized countries. Furthermore, in these high-risk settings, incidence densities of infections associated with the use of invasive devices (central vascular lines, ventilators and urinary catheters) are on average at least three-fold higher in low- and middle-income than in high-income countries (Figures 3.4 and 4.3). Pooled incidence density of CR-BSI and VAP in some developing countries were even shown to be up to 19 and 16 times higher than those reported from Germany and the USA.[3] Newborns are also at higher risk of acquiring HCAI, with infection rates in developing countries three to 20 times higher than in high-income countries.[205]

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Interestingly, UTI, especially related to urinary catheter use, is the most frequent infection detected hospital-wide in mixed patient populations in high-income countries. However, this type of infection has usually less severe consequences than other device-associated infections in terms of attributable mortality, related complications, and associated costs. Conversely, in low- and middle-income countries, SSI is the most frequent HCAI and affects up to one-third of operated patients. Frequencies reported for SSI are probably largely underestimated as, according to some studies, most are detected through post-discharge surveillance, which is very difficult to perform in developing countries.[32-38] SSI can prolong hospital stay up to 21 days in settings with limited resources.[230] In addition, it can bring a huge burden in terms of medium-term sequelae, personal suffering for the patient, and additional financial costs.

With regard to data availability, this report shows that information at the national level is regularly provided by several national surveillance systems and international networks in high-income countries. By contrast, very few national studies are available from low- and middle-income countries and the vast majority has no regular HCAI reporting system in place. Furthermore, even when considering studies related to single institutions, data are not available for many developing countries and some regions are poorly represented overall (Figure 4.1).

Although national figures on the burden of HCAI are available only for a few countries, based on data from Europe and the USA, it can be estimated that hundreds of millions of patients suffer from HCAI every year worldwide. However, it is important to note that infections acquired by health-care workers, data on outbreaks and blood-borne pathogens transmitted through transfusion, contaminated injections, and other procedures are not included in these estimates. For this reason, and because of reporting gaps even when surveillance systems are in place, the burden of HCAI is certainly greatly underestimated.

Raw data related to the number of affected patients and number of episodes per patient, together with a valid and accurate denominator (e.g. number of patients hospitalized for more than 48 hours) are not available from most countries. In addition, no system exists to collate these data on a global level, as is the case for other diseases annually reported by WHO. This is mainly due to constraints inherent to HCAI surveillance that include: the complexity of HCAI diagnosis (including lack of specific diagnostic tests, such as those available for human immunodeficiency virus (HIV), tuberculosis, and malaria); neglected use of standardized

definitions; lack of expertise and dedicated personnel; and the overall lack of financial resources to invest in this field. Further research is very much needed to identify mathematical models in order to obtain more predictive global estimates of HCAI. Although these should be partly based on findings from published epidemiological reports, the reliability of the study results must be considered as the quality can be very poor, particularly those conducted in developing countries. In addition, minimum requirements and standards should be set to allow countries to establish robust surveillance systems and report national figures. Case definitions need to be homogenized, together with the method of calculating the denominator, e.g. calculation of days at-risk until the first infectious episode or for the entire period of hospitalization. Adaptation of definitions to make HCAI detection more feasible in settings with limited resources should be considered and validated through scientifically sound investigations. Standardization would help to gather a more comprehensive picture and to optimize inter-hospital and international comparisons. Ideally, countries should adopt definitions and methods used by prominent surveillance networks, such as HELICS, NHSN, KISS and INICC. It would be also important to encourage these networks to join their efforts and use the same definitions, and even to explore possibilities to merge their data on a regular basis.

Evaluation of the key determinants of HCAI burden is complex, but it remains an essential step to identify strategies and measures for improvement. In advanced settings in high-income countries, HCAI may occur as a potentially expected adverse event of sophisticated care techniques and treatments typical of modern medicine. However, it is also evident that frequently it represents a health-care delivery system failure. Despite the broader availability of resources in these settings, awareness and knowledge of HCAI are often poor, and well-known, evidence-based, infection prevention and control strategies could be enforced and implemented more effectively.

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In developing countries, the nature of this problem is partially different because, in addition to general determinants similar to high-income countries, a combination of numerous unfavourable factors play an important role to increase the risk of HCAI. These are much more inherent to the situation and reality of these countries, such as poor hygiene and sanitation, lack or shortage of basic equipment, inadequate infrastructures, unfavourable social background, and a population largely affected by malnutrition and other types of infection and/or diseases.

Data from this report highlighting the serious burden of HCAI bring strong evidence that these determinants, as well as surveillance issues, must be carefully assessed and tackled as much as possible at all levels if any significant progress is to be made in the future. Table 6.1 summarizes the most relevant actions and perspectives for the improvement of HCAI surveillance and control.

Table 6.1
Key solutions and perspectives for improvement of HCAI surveillance and control

Solutions and perspectives for improvement
• Identifying local determinants of the HCAI burden. • Improving reporting and surveillance systems at the national level. • Ensuring minimum requirements in terms of facilities and dedicated resources available for HCAI surveillance at the institutional level, including microbiology laboratories' capacity. • Ensuring that core components for infection control are in place at the national and health-care setting levels. • Implementing standard precautions, particularly best hand hygiene practices at the bedside. • Improving staff education and accountability. • Conducting research to adapt and validate surveillance protocols based on the reality of developing countries. • Conducting research on the potential involvement of patients and their families in HCAI reporting and control.

Robust evidence exists that HCAI can be prevented and the burden reduced by as much as 50% or more.[41,173,295-298] Solid recommendations have been issued by national and international organizations,[7,251,299-305] but their application need to be strengthened and accompanied by performance monitoring both in high-, low- and middle-income countries. Furthermore, this body of evidence has accumulated mostly through studies conducted in industrialized countries and these strategies may

not always be applicable to settings with limited resources and different social and cultural backgrounds. However, it is noteworthy that very encouraging results from an increasing number of infection control interventions and programmes implemented in developing countries have been reported over the last decade. For instance, ICUs participating in the surveillance and infection control programmes coordinated by INICC have documented a substantial decrease of CR-BSI and CR-UTI over recent yea rs.[137-139,141,144,147,170,171,196] In addition, adaptations of hand hygiene promotion strategies have proved to be feasible and successful to improve practices[187,306-308] and, in several cases, to reduce HCAI[196,236,309] in settings with limited resources.

It is imperative that core components for infection prevention and control be put in place before any specific measures or "bundles" are implemented, and these were recently identified at the institutional level by WHO.[310] Among these, very important aspects concern the implementation of standard and isolation precautions,[299,301,305] environmental cleaning,[311,312] water and sanitation in health-care settings,[311] sterilization and disinfection procedures,[313,314] and infectious waste and sharp disposal, including other specific measures for injection safety.[311,315,316] Antimicrobial resistance (http://www.who.int/topics/drug_resistance/en/) should also be tackled with appropriate multi-disciplinary strategies, including infection control measures, as health care-associated pathogens often carry patterns of multi-drug resistance, well known to bring more virulence.[317]

By definition, HCAI affects also health-care workers and the promotion of protective measures and best practices should be among key priorities to reduce the burden of HCAI.[318] Staff education is a key element of all multimodal approaches and requires relatively limited efforts. It is now recognized that the basic principles of infection control should be included in the curricula of medical, nursing, and other healthcare professions and WHO has taken the initiative to issue guidelines for their content.[319,320] Finally, and most importantly, HCAI must be treated as a priority patient safety issue within comprehensive approaches to be tackled effectively. These include quality improvement and reporting and learning mechanisms, visible commitment by decision- makers and health-care administrators, increased individual accountability among health-care workers and, possibly, patient involvement.[321]

WHO Patient Safety actively works towards establishing the most effective ways in which to improve global health care and save lives lost to HCAI (http://www.who.int/patientsafety/en/). Among these, the *Clean Care is Safer Care* programme is aimed at reducing the burden of HCAI worldwide with improvement of hand hygiene practices as the core component (http://www.who.int/gpsc/en/). WHO Patient Safety closely collaborates with other programmes at headquarters, including regional and country offices supporting Member States, to reduce HCAI by assisting with the assessment, planning, and implementation of infection prevention and control policies, and timely actions at national and institutional levels.

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APPENDIX

Search terms

Cross-infection [MeSH Term], nosocomial infection, nosocomial infections, hospital acquired infection, hospital acquired infections, hospital-acquired infection, hospital-acquired infections, health care associated infection, health care associated infections, health care-associated infection, health care-associated infections, and infection control [Mesh Term], infection control, bloodstream infection, bloodstream infections, nosocomial bacteremia, nosocomial bacteraemia, nosocomial septicemia, nosocomial septicaemia, device-associated infection, device-associated infections, urinary tract infection, urinary tract infections, surgical site infection, surgical site infections, wound infection, wound infections, ventilator-associated pneumonia, ventilator associated pneumonia, hospital-acquired pneumonia, hospital acquired pneumonia, developing country, developing countries, and developing countries [Mesh Terms], developed country, developed countries, and developed countries [Mesh Terms] and names of the countries individually.

WHO regional medical databases

Western Pacific Region Index Medicus (WPRIM); Latin America and Caribbean Health Sciences (LILACS); African Index Medicus (AIM); Index Medicus for the Eastern Mediterranean Region Database (IMEMR); Index Medicus for the South-East Asian Region (IMSEAR-HELLIS).

World Health Organization

Patient Safety

A World Alliance for Safer Health Care

World Health Organization
20 Avenue Appia
CH – 1211 Geneva 27
Switzerland
Tel: +41 (0) 22 791 50 60

Email
savelives@who.int
Please visit us at:
www.who.int/patientsafety/en/
www.who.int/gpsc/en

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