Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis

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Summary

Background

Health-care-associated infection is the most frequent result of unsafe patient care worldwide, but few data are available from the developing world. We aimed to assess the epidemiology of endemic health-care-associated infection in developing countries.

Methods

We searched electronic databases and reference lists of relevant papers for articles published 1995—2008. Studies containing full or partial data from developing countries related to infection prevalence or incidence—including overall health-care-associated infection and major infection sites, and their microbiological cause—were selected. We classified studies as low-quality or high-quality according to predefined criteria. Data were pooled for analysis.

Findings

Of 271 selected articles, 220 were included in the final analysis. Limited data were retrieved from some regions and many countries were not represented. 118 (54%) studies were low quality. In general, infection frequencies reported in high-quality studies were greater than those from low-quality studies. Prevalence of health-care-associated infection (pooled prevalence in high-quality studies, 15·5 per 100 patients [95% CI 12·6—18·9]) was much higher than proportions reported from Europe and the USA. Pooled overall health-care-associated infection density in adult intensive-care units was 47·9 per 1000 patient-days (95% CI 36·7—59·1), at least three times as high as densities reported from the USA. Surgical-site infection was the leading infection in hospitals (pooled cumulative incidence 5·6 per 100 surgical procedures), strikingly higher than proportions recorded in developed countries. Gram-negative bacilli represented the most common nosocomial isolates. Apart from meticillin resistance, noted in 158 of 290 (54%) Staphylococcus aureus isolates (in eight studies), very few articles reported antimicrobial resistance.
Interpretation

The burden of health-care-associated infection in developing countries is high. Our findings indicate a need to improve surveillance and infection-control practices.

Funding

World Health Organization.

Introduction

Health-care-associated infections are deemed the most frequent adverse event threatening patients' safety worldwide.\(^1\)\(^–\)\(^3\) However, reliable estimates of the global burden are hampered by a paucity of data adequately describing endemic infections at national and regional levels, particularly in resource-limited settings.\(^4\) In countries where less than 5% of the gross national product is spent on health care, and workforce density is less than five per 1000 population,\(^5\) other emerging health problems and diseases take priority.\(^6\) The epidemiological gap leading to the absence of reliable estimates of the global burden is mainly because surveillance of health-care-associated infection expends time and resources and needs expertise in study design, data collection, analysis, and interpretation. Very few countries of low and middle income have national surveillance systems for health-care-associated infections. Data from the International Nosocomial Infection Control Consortium,\(^7\) and findings of two systematic reviews on hospital-acquired neonatal infections\(^8\) and ventilator-associated pneumonia,\(^9\) suggested not only that risks of health-care-associated infection are significantly higher in developing countries but also that the effect on patients and health-care systems is severe and greatly underestimated.

The aim of this systematic review and meta-analysis is to assess the burden of endemic health-care-associated infection in developing countries by collation of available data from published studies on epidemiology. We also aim to investigate constraints linked to surveillance of health-care-associated infection in resource-limited settings and identify perspectives for improvement.

Methods

Search strategy and selection criteria

We undertook a literature search and review process according to a protocol designed before data collection. We aimed to identify studies on the epidemiology of health-care-associated infection in developing countries, with a particular focus on the most frequent bacterial
infections—urinary-tract infection, surgical-site infection, bloodstream infection, hospital-acquired pneumonia, and ventilator-associated pneumonia. We searched Medline for reports published between January, 1995, and December, 2008, with no language restriction. We used a comprehensive list of terms (panel 1), including MeSH terms “cross infection”, “infection control”, and “developing countries”, together with individual names of countries of low and middle income, according to the 2008 World Bank classification. We applied the same search strategy to the Cochrane database to identify any published reviews, and we searched WHO regional medical databases (panel 1). Furthermore, we consulted Embase but our search did not yield additional publications.

Panel 1
Detailed search strategy and WHO databases

Search terms

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); and Index Medicus for the South-East Asian Region (IMSEAR-HELLIS).

One of us (SBN) screened abstracts of retrieved references for potentially relevant studies from developing countries, containing either full or partial data for proportions of overall health-care-associated infection and health-care-associated urinary-tract, surgical-site, and bloodstream infections and hospital-acquired and ventilator-associated pneumonia, and the microbiological causes of these infections. We excluded duplicate references, studies reporting outbreaks or including community-acquired infections, and publications reporting the same data. We obtained the full text of potentially relevant studies and two of us (SBN and BA)
scrutinised these reports independently. We also screened reference lists of all reviewed studies for further eligible publications.

Data extraction

Extracted data included: authors; year of publication; country or countries where the study was done; timescale; setting and scope of study; sample size; type of patient population (adult, neonatal, and paediatric); level of risk (high-risk patients, those admitted to intensive-care units [ICUs], burn and transplant recipients vs mixed populations, including individuals admitted to other lower risk areas); type of surveyed infection (overall health-care-associated infection, including at least the four most frequent infections [urinary-tract, surgical-site, and bloodstream infections, and hospital-acquired or ventilator-associated pneumonia]); surveillance methods; definitions used for diagnosis; reported infection prevalence or cumulative incidence data and corresponding denominators; microbiological isolates; wound contamination class and type of surgical-site infection; and antimicrobial resistance. We only judged microbiological data suitable for assessment when the number of bacterial isolates was reported. Selected studies used variably the terms “central venous catheter-associated”, “central venous catheter-related”, “central line-associated”, or “catheter-related bloodstream infection”; thus, we chose to use catheter-related bloodstream infection as a generic term throughout this present report when referring to these different categories. We further stratified studies into six regions (Africa, the Americas, Europe, southeast Asia, eastern Mediterranean, and western Pacific), according to WHO classification. After in-depth review and data entry into a dedicated database, we classified studies as high quality when the following predefined criteria were met: prospective design; use of standardised definitions (ie, according to the US Centers for Disease Control and Prevention National Nosocomial Infection Surveillance [NNIS]/National Healthcare Safety Network [NHSN] system); detection of at least all four major infections for studies related to health-care-associated infections in general; and publication in a peer-reviewed journal.

Statistical analysis

We pooled data from both prevalence and incidence studies and summarised the results in the same unit. The prevalence of either infection or infected patients refers to the number of infection episodes or infected patients per 100 patients present in the hospital or ward at a given point in time. The cumulative incidence refers to the number of either 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 surgical-site infection, it is usually 30 days after surgery whereas for other infections it refers to the duration of hospital or ward stay. Infection incidence density refers to the number of infection episodes per 1000
patient-days or device-days; incidence density data were only available from studies undertaken in ICUs.

We reported ranges of prevalence, incidence, and density and gave median values when calculation of pooled infection frequencies or densities was not possible. For studies reporting the same outcome measures and using the same methods, we pooled data when the appropriate denominator was available. We calculated pooled proportions and densities with Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ, USA). Models were systematically applied with random effects. We measured heterogeneity with the I² statistic (values of 25%, 50%, and 75% represented low, medium, and high heterogeneity, respectively). We compared groups of high-quality and low-quality studies with Cochran’s test. We used the two-sample Kolmogorov-Smirnov non-parametric test to compare frequencies of surgical-site infection with wound classification. When the number of available studies was greater than ten, we did meta-regressions to investigate the association between outcomes, year of publication, and proportion of gross domestic product dedicated to health per country. We judged p≤0.05 significant.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our search yielded 7719 abstracts, of which 271 published articles were eligible for inclusion. For 48 studies (18%), the full paper could not be accessed (n=19) or was not screened owing to language restrictions (n=29); three articles were further excluded at second reading because findings were duplicated in other publications (figure 1). 220 articles in English, French, German, and Spanish were included in the final analysis. Two additional systematic reviews were retrieved on neonatal health-care-associated infection and ventilator-associated pneumonia in developing countries; no review was available from the Cochrane database.
Mapping of retrieved studies revealed a scattered global picture (table 1). Health-care-associated infection was recorded poorly in some regions, particularly Africa and the western Pacific region. In regions with the most reports (Europe and the Americas), studies generally covered only a few countries (figure 2). Nine studies from four developing countries were undertaken at national level (13—21) and another 14 were multicentre country-specific studies (five related to health-care-associated infection in general, 22—26 nine to surgical-site infections). 27—35 136 (62%) were undertaken at a single hospital or on one ward and 110 (50%) were done in teaching hospitals. 118 of 220 studies (54%) were of overall low quality, according to our criteria.

Table 1

Health-care-associated infections in developing countries according to WHO region, patient population, and type of infection (1995—2008)

We identified 22 prevalence and 12 incidence studies reporting proportions of overall health-care-associated infection in mixed populations of patients (see Statistical analysis for explanation about units), 13—16,18,22—26,36—59 Prevalence of health-care-associated infection varied between 5·7 and 19·1 per 100 patients, and incidence was 1·7—23·6 per 100 patients (figure 3). Pooled prevalence and incidence of overall health-care-associated infection was 10·1 (95% CI 8·4—12·2) and 7·4 (4·4—12·2) per 100 patients, respectively, and the pooled prevalence of infected patients was 10·6 (8·1—13·9) per 100 patients. 11 (50%) prevalence studies reported proportions of infected patients or infection frequencies higher than 10·0 per 100 patients. 23,39,40,42—45,51—54 In this population of patients, 29% of health-care-
associated infections were surgical-site infections, 24% affected the urinary tract, 19% were bloodstream infections, 15% were health-care-associated pneumonia, and 13% were other infections.

**Figure 3** Full-size image (24K) Download to PowerPoint

Box plots indicate range of infection prevalence and cumulative incidence for first and third quartile. Medians are indicated as a black line. Whiskers indicate lower and upper end of distribution. Infection proportions are shown as infections per 100 patients (Inf/100 pts) and infected patients per 100 patients (Inf pts/100 pts).

A high level of heterogeneity was noted between prevalence studies that included data for overall health-care-associated infection ($I^2=97·4\%$). However, only 41% (9/22) of reports met high-quality criteria.$^{18,23,25,40,43—45,51,54}$ Pooled prevalence of overall health-care-associated infection was 15·5 per 100 patients (95% CI 12·6—18·9) in high-quality studies and 8·5 (7·1—10·0) in low-quality studies ($p<0·0001$). Similarly, the proportion of infected patients was higher in high-quality than low-quality studies (13·5 vs 7·2 per 100 patients; $p=0·0007$).

Overall health-care-associated infection and device-associated infection densities in adult high-risk patients were reported in 38 studies.$^{60—97}$ Density of overall health-care-associated infection ranged from 9·0 to 91·7 episodes per 1000 patient-days. In studies undertaken in ICUs, pooled cumulative incidence and density were 34·7 per 100 patients (95% CI 23·6—47·7) and 47·9 per 1000 patient-days (36·7—59·1), respectively (figure 4A); high heterogeneity was detected in the results of these studies ($I^2=99·6\%$ and 99·4%, respectively). In a study undertaken in 55 ICUs from eight countries, overall ICU-acquired, device-associated infection density was as high as 22·5 episodes per 1000 patient-days.$^{72}$ In a multicentre ICU study from Argentina,$^{62}$ and in other studies undertaken at oncology and neurology units in Brazil,$^{92}$ and Turkey,$^{97}$ density of health-care-associated infection even exceeded 80 episodes per 1000 patient-days.
Figure 4 Full-size image (66K) Download to PowerPoint

Pooled overall health-care-associated and device-associated infection densities in adult intensive-care units in developing countries, 1995—2008

(A) HAI=health-care-associated infection. Density=HAI episodes per patient-day. N=overall number of patient-days. (B) CR-BSI=catheter-related bloodstream infection. Density=CR-BSI episodes per catheter-day. N=overall number of catheter-days. (C) CR-UTI=catheter-related urinary-tract infection. Density=CR-UTI episodes per urinary catheter-day. N=overall number of urinary catheter-days. (D) VAP=ventilator-associated pneumonia. Density=VAP episodes per ventilator-day. N=overall number of ventilator-days.

In 31 studies, 60—90 densities of specific types of ICU-acquired device-associated infections in adults varied between 1·7 and 44·6 per 1000 catheter-days for catheter-related bloodstream infections, 1·4 and 23·0 per 1000 urinary catheter-days for catheter-related urinary-tract infections, and 3·2 and 56·9 per 1000 ventilator-days for ventilator-associated pneumonia. Figures 4B—4D show pooled densities for these three types of infection, 60—63, 65, 66, 68, 72—74, 78, 79, 81, 83, 86, 87, 89, 90 and table 2 presents a comparison of densities reported by the US NNIS/NHSN, 98, 99 and the German hospital infection surveillance system. 100, 101 A high level of heterogeneity was detected in studies reporting catheter-related bloodstream infections ($I^2=97·2\%$), catheter-related urinary-tract infections ($I^2=98·2\%$), and ventilator-associated pneumonia ($I^2=97·2\%$). Quality of incidence studies undertaken in ICUs was judged high in most cases (23/36, 64%). While investigating the association between infection incidence densities and year of publication of the studies included in the meta-analysis (1997—2008; figure 4), a significant decrease over time was recorded for the incidence density of overall health-care-associated infections ($p=0·0001$), catheter-related bloodstream infections ($p=0·0230$) and catheter-related urinary-tract infections ($p=0·0008$).

Table 2

Comparison of device-associated infection densities in adult ICUs from developed and developing countries, 1995—2008
In 40 published studies, epidemiology of health-care-associated infection was reported for neonates and children \(\text{(table 1)}\). Cumulative incidence of health-care-associated infections and of infected patients on paediatric wards or in children's hospitals was \(0.9-17.7\) per 100 patients, respectively; respective pooled incidences were 5.7 (95% CI 2.3—13.1) and 10.9 (2.8—34.5) per 100 patients. Densities of overall health-care-associated infection in paediatric ICUs were \(1.6-46.1\) per 1000 patient-days, and in neonatal units they were \(15.2-62.0\) per 1000 patient-days. \(109-121\) Densities of ventilator-associated pneumonia ranged from \(4.4\) to \(143\) episodes per 1000 ventilator-days (median \(28.0\) [IQR \(10.9-88.3\)]), and densities of catheter-related bloodstream infections were between \(10.2\) and \(60.0\) episodes per 1000 catheter-days (median \(18.7\) [12.5—43.0]). \(112,113,115,117-119,121\) Data pooled from four comparable studies undertaken in Brazilian neonatal ICUs \(109-112\) revealed an overall incidence of health-care-associated infections of \(40.8\) infections per 100 patients (95% CI 16.1—71.1) and a density of \(30.0\) episodes per 1000 patient-days (25.0—35.0).

Of 101 studies in which specific types of infection were addressed, 57 (56%) focused on surgical-site infections. Reported cumulative incidence of these infections ranged from \(0.4\) to \(30.9\) per 100 patients undergoing surgical procedures and from \(1.2\) to \(23.6\) per 100 surgical procedures \(\text{(figure 5A)}\). \(17,27-35,55,122-161\) Pooled cumulative incidence of surgical-site infections was \(11.8\) per 100 patients undergoing surgical procedures (95% CI 8.6—16.0) and \(5.6\) per 100 surgical procedures (2.9—10.5), and a high level of heterogeneity was seen in these studies \((I^2=99.0\% \text{ and } 99.4\%, \text{ respectively})\). Median cumulative incidence of surgical-site infections in clean, clean-contaminated, contaminated, and dirty wounds were, respectively, \(7.6\) (range \(1.3—79.0\)), \(13.7\) (1.5—81.0), \(14.3\) (0.5—65.5), and \(39.2\) (0.2—100.0) episodes per 100 surgical procedures \(\text{(figure 5B)}\). \(17,122,124,127,128,131,137,139-141,143-148,150,153,155,157,158,160\) Proportions of surgical-site infections differed significantly between wound classes \(\text{(dirty vs clean, } p<0.0001; \text{ dirty vs clean-contaminated, } p=0.0006; \text{ dirty vs contaminated, } p=0.0291)\).

**Figure 5** Full-size image (42K) Download to PowerPoint

Cumulative incidence of surgical-site infections overall \(\text{(A)}\) and according to wound classification \(\text{(B)}\) in developing countries, 1995—2008

Box plots contain results for first and third quartile. Medians are indicated as a black line. Whiskers indicate lower and upper limits of distribution. Incidence is reported as surgical-site infection episodes, either per 100 surgical patients or per 100 surgical procedures.
Information on pathogens causing health-care-associated infections in general was available from 28 studies; 18, 22, 23, 25, 38, 40, 43—45, 51, 58, 65, 66, 68, 81, 85, 86, 92, 93, 97, 162—169. 18 included microbiological data specifically related to surgical-site infections, ventilator-associated and health-care-associated pneumonia, and bloodstream infections (table 3). 64, 76, 84—86, 122, 132, 138, 140, 149—151, 156, 158, 170, 171 Gram-negative bacilli represented the most common nosocomial isolates, both in mixed populations and in high-risk patients. The most frequent single pathogens were Staphylococcus aureus in mixed populations and Acinetobacter spp in high-risk patients. Acinetobacter spp was the second most frequent pathogen identified for ventilator-associated pneumonia and, unexpectedly, bloodstream infections. S. aureus was the most frequent single pathogen causing surgical-site and bloodstream infections. Gram-negative bacilli were isolated in just under half of surgical-site infections (table 3). In view of the few isolates and heterogeneous geographic distribution, country-specific and region-specific pathogen distribution was not investigated. Apart from meticillin resistance, reported in 54% of S. aureus isolates (158/290) from eight studies, 43—45, 58, 138, 149, 151, 164 very few articles included data about antimicrobial resistance patterns and no assessment of this aspect was done.

Table 3

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Bacterial isolates identified in health-care-associated infections from developing countries, 1995—2008*

Discussion

In this systematic review and meta-analysis, we have shown that endemic health-care-associated infection represents a major burden and safety issue for patients in the developing world, with an even greater epidemiological relevance than in developed countries. Compared with average prevalence of health-care-associated infection in Europe (reported as 7·1 per 100 patients by the European Centre for Disease Prevention and Control) 172 and estimated incidence in the USA (4·5 per 100 patients in 2002), 173 pooled prevalence of health-care-associated infection in resource-limited settings is substantially higher, particularly in high-quality studies (15·5 per 100 patients).

The difference between developing and developed countries is even more striking when considering incidence of ICU-acquired infection (pooled density 47·9 per 1000 patient-days in developing countries), which is estimated to be 13·6 per 1000 patient-days in the USA. 173 Although invasive devices represent an unavoidable infection risk for the critically ill patient, this risk goes well beyond an acceptable level in the developing world, especially for incidence
of ventilator-associated pneumonia and catheter-related bloodstream infections in both adult and paediatric patients. In our review, pooled densities of device-associated infection in critically ill adult patients from comparable studies were two to eight times higher than those reported by the US NNIS/NHSN\textsuperscript{98, 99} and the German hospital infection surveillance system (table 2).\textsuperscript{100, 101} Pooled data from some low-income and middle-income countries even showed densities up to 19 and 16 times higher for catheter-related bloodstream infections and ventilator-associated pneumonia, respectively. Our findings also indicated that ventilator-associated pneumonia is the most frequent type of health-care-associated infection in this population of patients (figure 4D).\textsuperscript{9}

Zaidi and colleagues\textsuperscript{8} reported neonatal infection rates three to 20 times higher in resource-limited countries than in industrialised nations. Our analysis confirms these data, with the finding that the density of overall health-care-associated infections in neonatal ICUs in some countries (eg, Brazil)\textsuperscript{109—112} is up to nine times higher than in the USA (6·9 infections per 1000 patient-days vs 15·2—62·0 infections per 1000 patient-days in our review).\textsuperscript{173} Importantly, very high rates of health-care-associated infection in neonatal and paediatric populations were noted not only in ICUs but also in some paediatric wards and children’s hospitals.\textsuperscript{103, 106, 107, 174}

Our findings indicate that surgical-site infection is both the most frequently studied and the leading health-care-associated infection hospital-wide in the developing world. The alarming global burden of avoidable complications resulting from unsafe surgery has been highlighted by WHO.\textsuperscript{175, 176} The frequency of surgical procedures complicated by surgical-site infection was significantly higher in our study of developing nations compared with those recorded in high-income countries (pooled cumulative incidence 5·6 per 100 surgical procedures in our study). For example, in a nationwide study undertaken in the USA,\textsuperscript{177} the cumulative incidence of surgical-site infection was 2·6 per 100 surgical procedures; similarly, it was 2·9 per 100 surgical procedures in different European countries,\textsuperscript{178} and 1·6 per 100 procedures in Germany.\textsuperscript{100} Frequencies of surgical-site infection according to wound class were very high in all categories when compared with data reported in the USA.\textsuperscript{179}

Assessment of microbiological patterns of health-care-associated infection was based on only a few isolates. Therefore, we should be cautious about attributing a role to some microorganisms as causative pathogens of specific health-care-associated infections. Limitations in microbiological assessment are highlighted by the paucity of information on antimicrobial resistance.\textsuperscript{180} Apart from the high level of meticillin resistance seen in \textit{S aureus} isolates, we could not provide information on other resistance patterns in our present review.

What are the important determinants of a high burden of health-care-associated infection in developing countries? With available evidence, this question is difficult to answer, particularly
since information on risk factors is scanty (data not shown). However, potential determinants include inadequate environmental hygienic conditions; poor infrastructure; insufficient equipment; understaffing; overcrowding; paucity of knowledge and application of basic infection-control measures; prolonged and inappropriate use of invasive devices and antibiotics; and scarcity of local and national guidelines and policies. Although judged the most important measure for prevention of microbial transmission during patient care, hand hygiene is very often neglected by health-care workers in settings with limited resources, as shown repeatedly by adherence of less than 20% in a growing number of reports.157,183–188

Another widespread unsafe practice in developing countries is reuse of equipment (needles, gloves) because resources are scarce. In 2000, WHO estimated that 39·3% of injections in developing countries were done with reused equipment.189 The main outcome of contaminated injections was an estimated 21 million hepatitis B infections, 2 million hepatitis C infections, and 260 000 HIV infections. Sharing of syringes caused a large-scale nosocomial outbreak of HIV affecting 39 patients at two renal dialysis centres in Egypt.190 Although these types of infection are not the topic of our report, bacterial pathogens can possibly be transmitted through the same route.

While mapping the endemic situation of health-care-associated infection in developing countries, we noted a paucity of available data and a fragmented picture, with some regions and many countries poorly represented (figure 2). National or multicentre surveillance reports were available from only a few low-income and middle-income countries, whereas 43 national and 50 multicentre studies undertaken in the developed world were published, according to the same search criteria (data not shown). The paucity of national reports accords with findings of a survey done by WHO, in which only 23 of 147 developing countries (16%) reported a functioning national surveillance system.191 Furthermore, according to the European Centre for Disease Prevention and Control, only four of 26 (15%) countries of low and middle income in Europe have implemented surveillance protocols for health-care-associated infection at national level.172

The emerging picture clearly indicates that major difficulties exist for implementation of surveillance for health-care-associated infection in developing countries. The main reasons can be traced to an absence of expertise and dedicated human and financial resources and to the existence of other important health-care priorities (panel 2). Use of standardised definitions is limited by the scarcity and frequent unreliability of microbiological data and other diagnostic procedures, inaccuracy of information from patients' records, and a paucity of electronic records and software or databases for surveillance of health-care-associated infection. Furthermore, expertise in data interpretation—and a leadership commitment to use data for raising awareness and intervention—is sometimes absent.

Panel 2
Surveillance constraints and perspectives for improvement and research of health-care-associated infection in developing countries

**Appropriate surveillance constraints**

- Paucity of dedicated human resources and funds
- Scarcity of expertise in epidemiology and infection control
- Difficulties in application of standard definitions:
  - limited expertise to distinguish between infection, colonisation, and contamination
  - shortage of reliable microbiological and other diagnostic methods
  - poor-quality information from patients’ records
  - need to evaluate clinical evidence
- Absence of skills for data interpretation and use
- Sparse or insufficient microbiological laboratory capacity
- Existence of different payer sources

**Perspectives for improvement and research**

- Improve reporting of information in clinical records
- Ensure minimum requirements in terms of facilities and resources available for surveillance
- Improve capacity-building for clinical microbiological laboratories
- Ensure that core components for infection control are in place
- Promote staff education on infection control and surveillance of health-care-associated infection
- Undertake research to adapt and validate definitions of health-care-associated infection and protocols for its surveillance on the basis of the reality of developing countries
- Undertake research on patients’ and relatives’ education and involvement in detection and reporting of health-care-associated infection

About half of studies in our review were of overall low quality, mainly indicated by use of non-standardised definitions and suboptimum surveillance methods. For this reason, comparison of data from different studies proved to be challenging. Furthermore, about two-thirds of studies were undertaken at single hospitals or on one ward, and findings from these cannot be deemed representative of the endemic situation of health-care-associated infection in specific countries. Similarly, half of all studies were done in teaching hospitals, in which rates of health-care-associated infection are usually higher. Thus, generalisability of these data to all settings
is questionable. These technical constraints, and variations in settings, account at least partly for the reported heterogeneity in all study categories.

Despite our broad selection criteria and extensive search of several databases, only a fairly limited number of articles were retrieved by our literature search. Studies might have been done but not published or published in abstract form only. Moreover, although endemic rates of health-care-associated infection reported in intervention studies were included in this Article, further data could be available from non-population-based randomised clinical trials not retrieved by our search.

Overall health-care-associated infection has a great effect on health-care facilities, national health-care systems, and patients. Unfortunately, in studies retrieved by our search, findings related to increased length of stay and attributable mortality and costs associated with health-care-associated infection (data not shown) were fragmentary, differed strikingly between studies, and methods to calculate variables were seldom reported. For these reasons, we did not include information on this topic. Reliable and systematic data—specific to country and setting—about the effect of health-care-associated infection are needed urgently, including investigation of the relation between rates of health-care-associated infection and a country's gross domestic product. This area of research should be developed to inform policy makers about the most efficient use of available resources.

Our data have the potential to alert policy makers and decision makers to the fact that health-care-associated infection represents a hidden and serious burden for systems and patients alike. Since 2005, 88 UN member states of 147 developing countries (60%) have committed to reduce health-care-associated infection by signing the pledge of WHO's First Global Patient Safety Challenge, together with 36 governments from 46 developed countries (78%). Action is now required, and investment of human and financial resources is necessary; perspectives for improvement and research are proposed (panel 2). Setting up the core components for infection control identified by WHO could represent an important starting point to reduce the burden of endemic health-care-associated infection and guarantee better preparedness. In many cases, measures to prevent health-care pathogen transmission are low-cost, such as hand hygiene. Staff education is a key element, needing fairly limited efforts, and basic principles of infection control should be included in curricula of doctors, nurses, and other health-care professions. Relevant efforts are being made by international networks (eg, African Partnership for Patient Safety, Infection Prevention and Control African Network, International Federation of Infection Control, International Nosocomial Infection Control Consortium, Réseau International pour la Planification et l’Amélioration de la Qualité et de la Sécurité dans les Systèmes de Santé en Afrique) to build infection surveillance and control skills in developing countries, but apart from the International Federation of Infection Control and International Nosocomial Infection Control
Consortium, most are at an early stage. The European Centre for Disease Prevention and Control is also currently coordinating surveillance and infection-control activities in Europe, including some countries of low and middle income.

A finding of our meta-analysis was that reported incidence densities of health-care-associated infection, catheter-related bloodstream infection, and catheter-related urinary-tract infection in the ICU have fallen substantially over recent years. In most papers that reported these findings, regular surveillance data had been gathered by coordination of the International Nosocomial Infection Control Consortium.\textsuperscript{65, 66, 68, 72, 73, 78, 81, 86, 91} Therefore, the recorded decrease probably represents mostly the effect of surveillance per se and the effect of interventions implemented by this network.\textsuperscript{91,197—199} We also noted that most papers (162/220) retrieved through our review were published from 2003 onwards, thus indicating that surveillance activities have increased over the past 6 years.

An improvement in surveillance of health-care-associated infection is essential to record the size of this infection burden and the effect of interventions. Moreover, by itself, surveillance can lead to reduction in health-care-associated infection.\textsuperscript{100, 200} Further research to investigate adaptation and validation of standardised protocols and definitions affordable in developing countries is very much needed. Criteria for definition of health-care-associated infection, mostly on the basis of clinical elements, should be identified and their predictive values assessed by comparison with the most frequently used international definitions.\textsuperscript{11} In view of the important role of relatives and patients in health-care provision in developing countries, and to offset the effect of understaffing, affected individuals and their family members could be instructed to recognise and report signs of infection.\textsuperscript{201} For instance, this approach could help with detection of surgical-site infections, both during hospital stay and after discharge. An additional option is to prioritise process control,\textsuperscript{202} which is easy to undertake and could provide information on adherence to practices and the effect of interventions, thus potentially improving patients’ safety. As a result of improved surveillance of health-care-associated infection worldwide, and with the objective to raise awareness among policy makers and health-care workers, now could be the time to investigate epidemiological models that allow inclusion of health-care-associated infection in the list of major diseases causing morbidity, mortality, and disability, which are regularly reported by WHO and other institutions within global estimates of burden of disease.\textsuperscript{6}

\textbf{Contributors}

BA and DP had the idea for the project. SBN undertook searches of published work and did data extraction. BA reviewed data by independently reading the full articles. Statistical analysis and elaboration of figures was done by CC, WG, and HA. BA wrote the paper with important contributions from DP and input from SBN, CC, and HA. SLD provided valuable comments on
the report. All authors had full access to all data in the study and read and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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