The global burden of unsafe medical care: analytic modelling of observational studies

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ABSTRACT

Objective To contextualise the degree of harm that comes from unsafe medical care compared with individual health conditions using the global burden of disease (GBD), a metric to determine how much suffering is caused by individual diseases.

Design Analytic modelling of observational studies investigating unsafe medical care in countries' inpatient care settings, stratified by national income, to identify incidence of seven adverse events for GBD modelling. Observational studies were generated through a comprehensive search of over 16 000 articles written in English after 1976, of which over 4000 were appropriate for full text review.

Results The incidence, clinical outcomes, demographics and costs for each of the seven adverse events were collected from each publication when available. We used disability-adjusted life years (DALYs) lost as a standardised metric to measure morbidity and mortality due to specific adverse events. We estimate that there are 421 million hospitalisations in the world annually, and approximately 42.7 million adverse events. These adverse events result in 23 million DALYs lost per year. Approximately two-thirds of all adverse events, and the DALYs lost from them, occurred in low-income and middle-income countries.

Conclusions This study provides early evidence that adverse events due to medical care represent a major source of morbidity and mortality globally. Though suffering related to the lack of access to care in many countries remains, these findings suggest the importance of critically evaluating the quality and safety of the care provided once a person accesses health services. While further refinements of the estimates are needed, these data should be a call to global health policymakers to make patient safety an international priority.

INTRODUCTION

Most efforts to improve healthcare globally have focused on improving care for diseases that cause substantial morbidity and mortality, hoping to increase access to lifesaving therapies for the world's population. These efforts have begun to pay off, with increasing access to antimalarial drugs and antiretroviral therapies for patients with HIV.[1] However, institutionalising these gains will require focus on healthcare systems and their ability to deliver safe, effective care. This will be especially important in low-income and middle-income countries that are growing economically, and are looking to improve their health systems to care for a growing population.[2]

One lens through which to examine the functioning of healthcare systems is that of patient safety. Unsafe medical care—where patients are harmed by the medical care designed to help them—can have wide-ranging consequences.[3] Adverse events, or injuries as a result of medical care, lead to direct harm and waste, and have spillover effects on patient confidence in the healthcare system.[4] Many policymakers have primarily considered patient safety as an issue for high-income countries, where most of the population has access to basic healthcare. Indeed, estimates suggest that tens of thousands of citizens are injured, or die, due to medical errors in these countries.[5] While the lack of access to basic healthcare services in many countries remains a clear policy challenge in the context of health systems strengthening, the extent to which people face suffering due to unsafe care once accessing medical services is less obvious. In other words, the extent to which unsafe medical care—or adverse events resulting from medical care—is a problem for developing and transitional countries, once a person accesses these health services, is not well known.

WHO undertook the challenge of estimating the global burden of unsafe care as an essential step to guide global actions in strengthening health systems. The global burden of disease (GBD) is a standard metric used by policymakers throughout the globe to determine how much suffering is caused by individual diseases. Its application has been more recently expanded to examine events like road accidents and other public health dangers.[6] The GBD uses disability-adjusted life-years (DALYs) lost to quantify the morbidity and mortality associated with individual conditions and injuries.[6] Understanding the GBD of unsafe medical care would be helpful to quantify the degree to which the world's population encounters harm from unsafe healthcare interventions, allowing policymakers to better compare the DALYs lost from unsafe medical care to other causes of human suffering. Such data would allow policymakers to better prioritise the interventions likely to improve care and health for the world's citizens.

Therefore, in this study, we sought to answer three questions: first, what is the global burden of unsafe medical care? Second, to what extent does the issue of unsafe medical care affect low-income and middle-income countries (LMICs) compared with high-income countries (HICs)? And third, are there certain types of adverse events resulting from unsafe medical care that are particularly harmful that policymakers can target in order to eliminate unnecessary suffering?

METHODS

Definition of terms

For the purposes of this analysis, we consider *adverse events* as unsafe experiences in an inpatient hospital setting and are thereby contingent on people having access to these medical services. We then explore the 'clinical outcomes' (eg, the proportion of patients who die, the proportion who have an injury and the duration of an injury) of these adverse events in order to quantify the burden of these adverse events or unsafe medical practices on human suffering.

Identifying types of adverse events

In July 2007, WHO's Patient Safety programme convened a panel of international experts to discuss priorities for research on patient safety. The committee identified 20 topics that were of importance to patient safety, including structural factors, process of care and outcomes of unsafe care.[7] Of these twenty, twelve adverse events were candidates for estimating the GBD of unsafe medical care. After consultation with the WHO committee, and an exhaustive literature review, we excluded five of the 12 outcomes due to severe data limitations (eg, substandard or counterfeit drugs, unsafe blood products, unsafe injections, medical devices and surgical errors, although we captured some of the injuries from surgical care in venous thromboembolism or nosocomial pneumonia). Due to the inadequacy of these data on adverse events in the ambulatory care setting, we elected to focus only on inpatient adverse events. As such, the final set of seven outcomes or types of adverse events used for the analyses were: (1) adverse drug events (ADEs), (2) catheter-related urinary tract infections (CR-UTIs), (3) catheter-related blood stream infections (BSIs), (4) nosocomial pneumonia, (5) venous thromboembolisms (VTEs), (6) falls and (7) decubitus (pressure) ulcers. Hospitalisations resulting from these adverse events occurring to outpatients were excluded. Additionally, we excluded hospitalisations due to childbirth, as we had little information about adverse events among these hospitalisations.

Data sources

We used two primary sources of data: a literature review and findings from recent WHO-commissioned epidemiologic studies. First, the literature review strategy, as detailed in the online supplementary methodological appendix, was designed to be a comprehensive examination of both peer-reviewed and non-peer-reviewed studies that focused on the seven aforementioned adverse events of interest, the clinical features of the patients who were injured (eg, age), and their outcomes. For this analysis, we relied upon two separate literature reviews; the first was conducted in late 2007 through early 2008, and it was then repeated in 2011.[7] We supplemented the literature review with discussions with international experts in each topic area to ensure that key studies had been identified. The outcome of our literature review, including the specific studies that contributed incidence data for our models, is reported in the online supplementary methodological appendix.

The second data source for this study came from epidemiologic studies that were commissioned by WHO, which aimed to estimate the scale to which inpatient adverse events harmed patients. These studies have previously been described.[8 9] In brief, they consisted of the identification of adverse events by a two-stage medical record review: initial screening by nurses or junior physicians using 18 explicit screening criteria followed by a review by a senior physician for determination of the adverse event, its preventability and the resulting disability. The studies were conducted in 26 hospitals across eight low-income and middle-income countries in the Eastern Mediterranean and North African regions, and 35 hospitals across five countries in Latin America.[8 9] These studies also provided incidence data for our models.

Global burden of disease model

The GBD, run by WHO, uses disability-adjusted life years (DALYs) to measure morbidity and mortality due to a specific condition. The GBD DALYs model requires several key inputs: the number of people

affected, the age at which they are affected, and the clinical consequence of the adverse events, including the type of disability encountered (ie, clinical outcomes). Due to the paucity of data, we used a single average age per event, as opposed to standard GBD calculations done by age group and sex. The details of the model, including the formulae used, are detailed in the online supplementary methodological appendix.[10] For all our modelling approaches, we estimated each input separately for high-income versus low-income or middle-income (LMIC) countries (as defined by the World Bank).[11]

Identifying inputs for the GBD model

Incidence of adverse events: We estimated the incidence of each of our seven adverse events in a hospitalised population based on reported data from the literature review and epidemiologic studies described earlier. Given that there was a range of estimates for both HICs as well as for LMICs, we generally took the median incidence for each category as our 'best estimate' but allowed the entire range of incidence estimates in the Monte Carlo models (see analysis below).

Number of adverse events: In order to calculate the number of patients harmed due to adverse events after accessing medical services, we needed to estimate the number of hospitalisations that occur globally. To our knowledge, there is no single source where such data are available. Consequently, we used data from WHO, the World Bank, the Organisation for Economic Co-operation and Development (OECD), and others, including the Centers for Disease Control and Prevention in the USA to create these estimates. We used the median as our 'best estimate' for the number of hospitalisations, but allowed the modelling to take into account the entire range of data identified. For each of our seven outcomes or adverse events of interest, we multiplied the number of hospitalisations by the incidence to estimate the number of adverse events that occurred.

Demographics and outcomes of adverse events: We used data from the literature review to estimate demographics (eg, age and gender) of patients injured from an adverse event as well as their clinical outcomes (eg, the proportion of patients who typically die, the proportion that would suffer a long-term and a short-term injury, the duration of that injury, and the proportion that would suffer only minor injuries but no sustained disability). The distribution of age at the time of acquiring the condition and the outcomes for these injuries are shown in the online supplementary methodological appendix.

Calculating DALYs: To calculate DALYs, this required that we apply disability weights for the injuries or harms that are attributable to the seven adverse events explored in this analysis. We used WHO's GBD reports to identify disability weights for injuries when available; when not available, we identified the closest analogue or clinical condition for which there were disability weights available (see online supplementary methodological appendix). As is standard in these models, we assumed that the life expectancy was 81.3 years based on model life-table West Level 26, which has a life expectancy at birth of 82.5 for females and 80.1 for males.[12]

Analysis

Our primary analytic approach was to build a Monte Carlo simulation model with 1000 simulations for each of the seven adverse events within LMICs, and then separately for HICs. In these models, the best estimate was assumed to be the midpoint of the range with a triangular distribution. Therefore, we had 14 sets of Monte Carlo models (one for each of the seven adverse events for HICs and for LMICs). These models yielded the best overall aggregate estimate of the global burden of harm resultant from these adverse events. Moreover, the models produced distributions for each of the input variables, as well as each of the output variables (see online supplementary methodological appendix). Analyses were performed using SAS V.9.2.

RESULTS

We estimated that there were 117.8 million hospitalisations among the approximately 1.1 billion citizens in HICs in 2009, while there were 203.1 million hospitalisations among the 5.5 billion citizens of the LMICs. Hospitalisation rates for HICs were higher (mean 10.8 per 100 citizens per year) compared with those for LMICs (mean 3.7 per 100 citizens per year; see table 1).

Table 1 Hospitalisation rates in high, middle and low income countries

	High-income countries	Low-income and middle-income countries	Total
Hospitalisation rates*			N/A
Mean (95% CI)	10.8 (8.6 to 13.2)	3.7 (2.0 to 6.1)	
Total population	1 056 300 000	5 554 000 000	6 610 300 000
Total number of hospitalisations (estimated range)	117.8 M (94.3 M—143.4 M)	203.1 M (121.9 M—312.2 M)	421 M (225.5 M—616.3 M)

*Rates are per 100 citizens per year; M, million

Table 2 Incidence rates of adverse events among high versus low and middle-income countries

	High-income countries (%)	Low-income and middle- income countries (%)
Catheter-related UTI	1.1 (0.8 to 1.5)	2.0 (0.5 to 3.5)
Adverse drug events	5.0 (2.7 to 7.2)	2.9 (0.6 to 5.2)
Falls in the hospital	1.1 (0.3 to 2.0)	1.6 (1.3 to 2.0)
Catheter-related blood stream infection	0.4 (0.2 to 0.6)	0.4 (0.3 to 0.6)
Nosocomial pneumonia	0.8 (0.7 to 1.1)	0.4 (0.2 to 0.6)
Decubitus ulcers	2.4 (0.8 to 4.7)	2.4 (0.8 to 4.7)
Venous thromboembolisms	3.3 (1.9 to 4.8)	3.0 (1.0 to 4.8)
Overall incidence rate of adverse events	14.2	12.7

*Rates are means (95% CIs) per 100 hospitalisations per year.

We found large variations in the reported incidence of adverse events both within HICs and LMICs (see table 2). Of the seven adverse events analysed in the inpatient hospital setting, the most common type in HICs was adverse drug events with an incidence rate of 5.0% (CI 2.7% to 7.2%) while the most common in LMICs was venous thromboembolism (incidence rate of 3.0%, CI 1.0% to 4.8%). We found comparable incidence between HICs and LMICs of three types of adverse events: catheter-related blood stream infections, venous thromboembolism, and decubitus ulcers. We found lower rates of adverse drug events in LMICs compared with HICs (2.9% vs 5.0%) and nosocomial pneumonia (0.4% vs 0.8%), while rates of two types of adverse events (catheter-related urinary tract infection (CR-UTI) and falls) were higher in LMICs compared with HICs (see table 2). Based on these incidence data, we estimated that of every 100 hospitalisations, there were approximately 14.2 of these adverse events in HICs and 12.7 in LMICs. The age at which these adverse events occurred was generally 8 to 19 years higher in HIC (see online supplementary methodological appendix).

We estimate that there are approximately 16.8 million injuries annually due to these adverse events among hospitalised patients in HICs. LMICs, which have five times the population of HICs, experienced approximately 50% more adverse events (25.9 million, see table 3). The number of adverse events varied substantially depending on the type of event examined, and the estimates for each type of adverse event corresponded with wide confidence intervals. For instance, we estimated that there were approximately 1.4 million (95% CI 0.8 million to 2.0 million) catheter-related urinary tract infections among HICs, while there was a substantially higher number and rate in LMICs (4.1 million, 95% CI 0.5 million to 9.2 million).

Based on these findings, we estimate that there were 22.6 million DALYs lost due to these adverse events in 2009 (table 4). The number of DALYs lost were more than twice as high in LMICs (15.5 million) as they were in HICs (7.2 million). The biggest source of lost DALYs appeared to be venous thromboembolism (5.4 million DALYs in LMICs, 95% CI 1.1 million to 11.7 million) and 2.3 million in HICs (95% CI 1.1 million to 3.9 million). Although the underlying numbers of several of the infections were much smaller, they caused a comparable number of DALYs lost, often because the clinical outcomes were poor when these infections occurred (table 4).

For most of the adverse events explored in this study, the primary source of DALYs lost was premature death: 78.6% of all adverse events in HICs and 80.7% in LMICs. The proportion of DALYs lost due to short-term or long-term disability (as opposed to premature death) ranged from as little as 0.8% (catheter-related UTI) to a high of 32.9% (falls in the hospital) in all countries (table 4). While premature death constituted the primary source of DALYs lost, disability (both short and long term) were generally more common than death itself (see data presented in online supplementary methodological appendix).

DISCUSSION

Injuries secondary to adverse events from unsafe care present significant challenges to health systems across the globe.[13] We projected a collective 22.6 million

Table 3 Annual number of cases for selected adverse events

	High-income countries	Low-income and middle-income countries
Catheter-related UTI	1.4 M (0.8 M to 2.0 M)	4.1 M (0.5 M to 9.2 M)
Adverse drug events	5.8 M (2.7 M to 9.5 M)	6.0 M (0.6 M to 13.9 M)
Falls in the hospital	1.3 M (0.3 M to 2.5 M)	3.3 M (1.7 M to 5.7 M)
Catheter-related blood stream infection	0.5 M (0.1 M to 0.8 M)	0.9 M (0.4 M to 1.6 M)
Nosocomial pneumonia	1.0 M (0.7 M to 1.4 M)	0.9 M (0.3 M to 1.7 M)
Decubitus ulcers	2.9 M (0.7 M to 6.2 M)	4.9 M (1.1 M to 12.1 M)
Venous thromboembolisms	3.9 M (1.9 M to 6.3 M)	6.0 M (1.2 M to 12.8 M)
Total	16.8 M	25.9 M

M, Million

Table 4 Disability-adjusted life-years (DALYs) lost and source of the DALYs, in 2009

	DALYs*	Short-term disability (%)	Long-term disability (%)	Premature death (%)
High-income countries				
Catheter-related UTI	402 (214–620)	2.2	0.1	97.7
Adverse drug events	779 (350–1332)	5.7	0.3	94.0
Falls in the hospital	27 (6–51)	27.5	6.0	66.5
CR blood stream infections	1126 (328–2088)	3.0	0.2	96.8
Nosocomial pneumonia	2545 (1673–3703)	1.4	0.0	98.5
Decubitus ulcers	134 (58–268)	5.9	4.4	89.8
Venous thromboembolisms	2282 (1054–3855)	28.2	7.4	64.4
Total	7208 (5371–9271)	15.7	5.7	78.6
Low-income and middle-income countries				
Catheter-related UTI	3420 (450–8012)	0.7	0.0	99.4
Adverse drug events	1435 (126–3453)	2.3	0.1	97.6
Falls in the hospital	76 (6–169)	26.9	5.9	67.2
CR blood stream infections	2150 (958–4065)	3.0	0.2	96.8
Nosocomial pneumonia	2674 (996–5403)	1.4	0.0	98.5
Decubitus ulcers	291 (104–652)	30.0	5.6	64.4
Venous thromboembolisms	5399 (1126–11 730)	26.8	7.0	66.1
Total	15 454 (9009–23 607)	14.1	5.2	80.7
Total (combined)				
Catheter-related UTI	3822 (844–8412)	0.8	0.0	99.4
Adverse drug events	2214 (807–4274)	3.4	0.2	96.7
Falls in the hospital	103 (29–199)	27.0	5.9	68.1
CR blood stream infections	3276 (1752–5379)	3.0	0.2	98.2
Nosocomial pneumonia	5219 (3226–8120)	1.4	0.0	99.1
Decubitus ulcers	426 (209–804)	13.8	4.8	82.7
Venous thromboembolisms	7681 (3115–14 034)	27.3	7.1	70.7
Total	22 644 (15 899–30 979)	14.4	5.3	80.2

*All DALY numbers are in thousands.
DALYs, disability-adjusted life years.

DALYs lost due to adverse events experienced by the world's hospitalised population. Compared with other conditions, the combination of these seven adverse events alone estimated in this study rank as the 20th leading cause of morbidity and mortality for the world's population. It is unlikely that these are 'new' previously undiscovered DALYs, but rather that they are captured within the injuries and deaths attributed to other conditions such as cardiovascular disease. We suspect that these DALYs resulting from unsafe medical care may be one of the reasons why patients are disabled or die from these other conditions.

While lack of access to healthcare, especially hospital care, is clearly a major source of ill health and poor outcomes, especially in low-income countries, our work focuses on the safety of care once a person has accessed the medical resources available to them. We are unaware of any prior effort to examine the global burden of unsafe care across multiple types of adverse events. WHO estimates that the global burden of unsafe injection practices was over 9.2 million DALYs lost per year in the year 2000 alone.[14] If we had included those estimates, the resultant GBD from unsafe care would have been over 33 million DALYs, placing it as the 14th leading cause of morbidity and mortality in the world, comparable to the burden from tuberculosis or malaria. Including adverse events that were not possible to include in this study due to data limitations, such as unsafe surgery, harm due to counterfeit drugs, unsafe childbirth and unsafe blood use, as well as safety issues with ambulatory care, would further raise these estimates substantially. A recent systematic review[15] found that healthcare-associated infections are ubiquitous and occur at much higher rates in low-income countries than in HICs. Although these investigators did not calculate the GBD of these infections, their data underscore and support our findings that adverse events once reaching a hospital setting are common and likely cause unnecessary suffering across the globe.

These findings should prompt policymakers across the globe to invest further into systematic data collection, as well as programmes to measure and improve the safety of the healthcare systems. While the lack of access to care presents substantial harm, it is important to maintain high standards for safety and quality within the healthcare systems that we subject patients to across the globe. Unsafe medical care may even

lead patients, especially in low-income countries, to opt out of using the formal healthcare system, thereby making unsafe care a potentially significant barrier to access for many of the world's poor. Such a phenomenon would suggest that the distinction between access and quality (or in this case, safety) may not be so clear. Finally, other costs of unsafe care, such as increased consumption of resources due to prolonged stay and extra care—and loss of wages and productivity—are important, and would benefit from further investigation.

Limitations

This work has important limitations. The primary one is the lack of availability of high-quality data. Although there are nearly five times as many people living in LMICs, the number of adverse events we calculated was only 50% higher, primarily due to the lower hospitalisation rates and the poor quality of data sources in LMICs (including medical records). These poor quality data sources lead to undercounting of adverse events that are often not recorded. Nevertheless, the number of DALYs per event was substantially higher, likely due to a combination of a younger age at which these events occur, and the worse outcomes that often result. While this limitation may raise concerns about the validity of our findings, we used data from a large number of sources, and reassuringly found a consistent rate of adverse events.

The paucity of data also limited our ability to run calculations per age group and sex, leading us to calculate average estimates. Additionally, the data limited our analysis to reporting the aggregate harm resulting from total adverse events as opposed to preventable adverse events. While estimating preventable harm would be valuable, there is even greater uncertainty about how much harm is preventable at any given time, and as technology and clinical care changes, the proportion of adverse events that are preventable, likely will, as well. While our estimates are imprecise, we believe that as more data on adverse events become available, WHO will be able to refine these estimates and track them over time.

Second, while there are several high-quality studies, few use standardised definitions or approaches to identifying adverse events. Therefore, the data we relied on all used slightly different approaches and likely lead to some degree of imprecision.

Third, we elected to use the same life expectancy value for all individuals, and although this has been controversial, it is the standard approach used by WHO. Had we chosen different life expectancies for different countries, we likely would have estimated a lower number of DALYs lost, especially for low-income and middle-income countries.

Fourth, we excluded publications not written in English, which may have affected the precision of our estimates. Nearly all major epidemiologic studies of adverse events from HICs over the past decade have found that they occur in 8–15% of hospitalised patients. Data from LMICs suggest that the rates are even higher. Further, we excluded studies that were clearly of low quality, including those that used non-standard methods (such as convenience samples), or had unclear denominators, or extremely small sample sizes. Whether and to what degree these exclusions biased our findings is unclear.

Fifth, as described above, key inpatient adverse events that the WHO Committee on Patient Safety viewed as important were excluded due to data limitations (eg, unsafe childbirth), leading us to underestimate the true burden of harm from unsafe medical care. Also, we excluded adverse events in the ambulatory setting, which recent data suggest are a major source of harm.

Finally, we lacked disability weights specifically designed for the injuries we examined attributable to our seven adverse events. However, most of the injuries did have clinically analogous events for which there were disability weights. In other words, we identified 'proxy' conditions for each adverse event, usually choosing diseases that affected the same organ system with a generally similar level of severity. We attempted to use the most conservative disability weight in the model, though we recognise that our efforts at matching are imperfect. For example, for catheter-related infections, we used the proxy condition of endocarditis which has a disability weight range from 0.17 to 0.32. This is more fully described in the online supplementary methodological appendix. WHO has a well designed and rigorous process for creating disability weights, and the potential impact of these results will likely spur them to create specific disability weights for these injuries.

Although our estimates are quite conservative, they still represent a relatively wide range of possible outcomes because of inadequate data. Poor quality data on health systems, especially on adverse events, hampered our ability to effectively calculate the number of DALYs lost due to unsafe care, especially within LMICs. Even in HICs, these data are not routinely measured and made publicly available,[16] hampering not only our ability to calculate their consequences, but also limiting the ability of clinical leaders and policymakers to track the potential impact of policies designed to increase the safety of healthcare. As LMICs prosper economically, it is hopeful that citizens will have greater access to medical services, and more encounters with the healthcare system. Without concomitant improvements in the safety of health systems, the number of injuries will likely grow.

CONCLUSION

Using a conservative approach, we estimated that there are at least 43 million injuries each year due to medical care, and that nearly 23 million DALYs are

lost as a consequence. A large majority of these injuries and harm occur in developing and transitional countries—and these numbers will likely grow. Given the magnitude of these effects, our findings suggest that to improve the health of the world's citizens, we will need to improve access to care and also to invest substantial focus on improving the safety of the healthcare systems that people access worldwide. When patients are sick, they should not be further harmed by unsafe care. This should be a major policy emphasis for all nations.

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Appendix:

The Global Burden of Unsafe Medical Care: An Observational Study

The World Alliance for Patient Safety commissioned a comprehensive review of the literature on patient safety in 2007. This review, conducted with the input of the committee on research for patient safety, identified 23 topics of patient safety. These included adverse events, which were postulated to cause substantial morbidity and mortality. From this review, we identified ten different types of adverse events on which to base our models (See Table 1 below). We further narrowed our search to exclude 5 of the 10 domains of adverse events, usually because adequate data on these topics were not widely available or were significantly outdated. Additionally, it became evident that the best data available were based on potential causes of harm due to medical care received within the hospital. Therefore, we excluded adverse events in the outpatient setting. We based our approach on the remaining seven types of adverse events. The case definitions are primarily based on how each of these adverse events are defined in the literature, accounting for modest variations among these definitions. When the studies had no case definition or were defined in ways that appeared to be very different than the cases as defined below, we generally excluded those studies.

Table 1. Domains of adverse events

1	Injuries due to counterfeit and/or substandard drugs*
2	Injuries due to medical devices*
3	Injuries due to medications
4	Injuries due to surgical errors*
5	Injury due to health-care associated infections a. Hospital-Acquired Infections : Nosocomial Pneumonia

	b. Hospital-Acquired Infections: Catheter-related Blood Stream Infections c. Hospital-Acquired Infections: Catheter-related Urinary Tract Infections
6	Injury due to unsafe injections / blood products*
7	Injuries at the time of childbirth for mother and child*
8	Injuries due to thrombo-embolism from medical care
9	Injuries from falls in the hospital
10	Injury due to pressure sores and decubitus ulcers

*These adverse events were excluded because of inadequate data available.

Summary of the Data from our Literature Review and Case Definitions

An iterative systematic literature review was performed at the Harvard School of Public Health (HSPH) between March 2008 and April 2011. Co-Investigators at HSPH, Brigham and Women's Hospital (BWH), and the Johns Hopkins Bloomberg School of Public Health first reviewed the data and then commented on and requested additional data. Countries were classified as either "low- or middle-income" (LMIC) or "high-income" (HIC) based on categorization by the World Bank. Country demographic and health statistics data were obtained from the World Health Organization, OECD, IMF, and World Bank "World Development Indicators."

Study staff consulted with trained librarians at Harvard University to develop an appropriate and comprehensive search strategy. Primary Medical Subject Headings (MeSH) terms were identified in collaboration with librarians, Co-Investigators, and study staff. Articles not written in English and before 1976 were excluded and the rest were screened for merit. Although we did not use a formal screening criteria, we excluded studies that were clearly of low quality, including those that used non-standard methods (such as convenience samples) or had unclear

denominators, or extremely small sample sizes. The *Global Burden of Disease: 2004 Update*, sponsored by the World Health Organization, was consulted to ensure the search strategy captured all pertinent publications.

The search examined the global burden of disease in five domains, for a total of seven (7) adverse events:

1. Adverse Drug Events
2. Hospital-Acquired Infections : Nosocomial Pneumonia
3. Hospital-Acquired Infections: Catheter-related Blood Stream Infections
4. Hospital-Acquired Infections: Catheter-related Urinary Tract Infections
5. Venous Thrombo-embolisms
6. Falls in the Hospital
7. Decubitus Ulcers

For each of the seven adverse events noted above, up to five types of data were collected from each publication: incidence, clinical outcomes, demographics, costs, and study design/setting. These data were used to project the number of people affected (both short-term and long-term), clinical outcomes (e.g., proportion of affected population who fully recover, have short-term disability, have long-term disability, or die due to unsafe care), life expectancy, and the disability-adjusted life years (DALYs). The details of the search and the yields are described below in the section on case definitions and search results. Moreover, we provide in the table below a summary of the primary data sources used for inputting incidence rates into our model for each of the aforementioned seven adverse events.

Our search highlighted the paucity of systematic global data available for our chosen adverse events. Particularly in LMICs, the variability in data was extensive and presented substantial challenges to our work. For example, rates of hospitalizations among these nations varied more than 10-fold. To be a truly robust indicator, the global burden of disease model requires more specific data on patient demographics, the number of people who are hospitalized, the severity of disability that results from adverse events, and the duration of injury, many of which were not directly available. We focused on data where they were available and made best estimates using existing data. For instance, given that the clinical outcomes of adverse events were generally not available for LMICs, we often assumed that these patients' outcomes would be no better than those for patients suffering identical injuries in HICs. Whenever we had to make estimates based on existing data, we sought to make the most conservative assumptions possible.

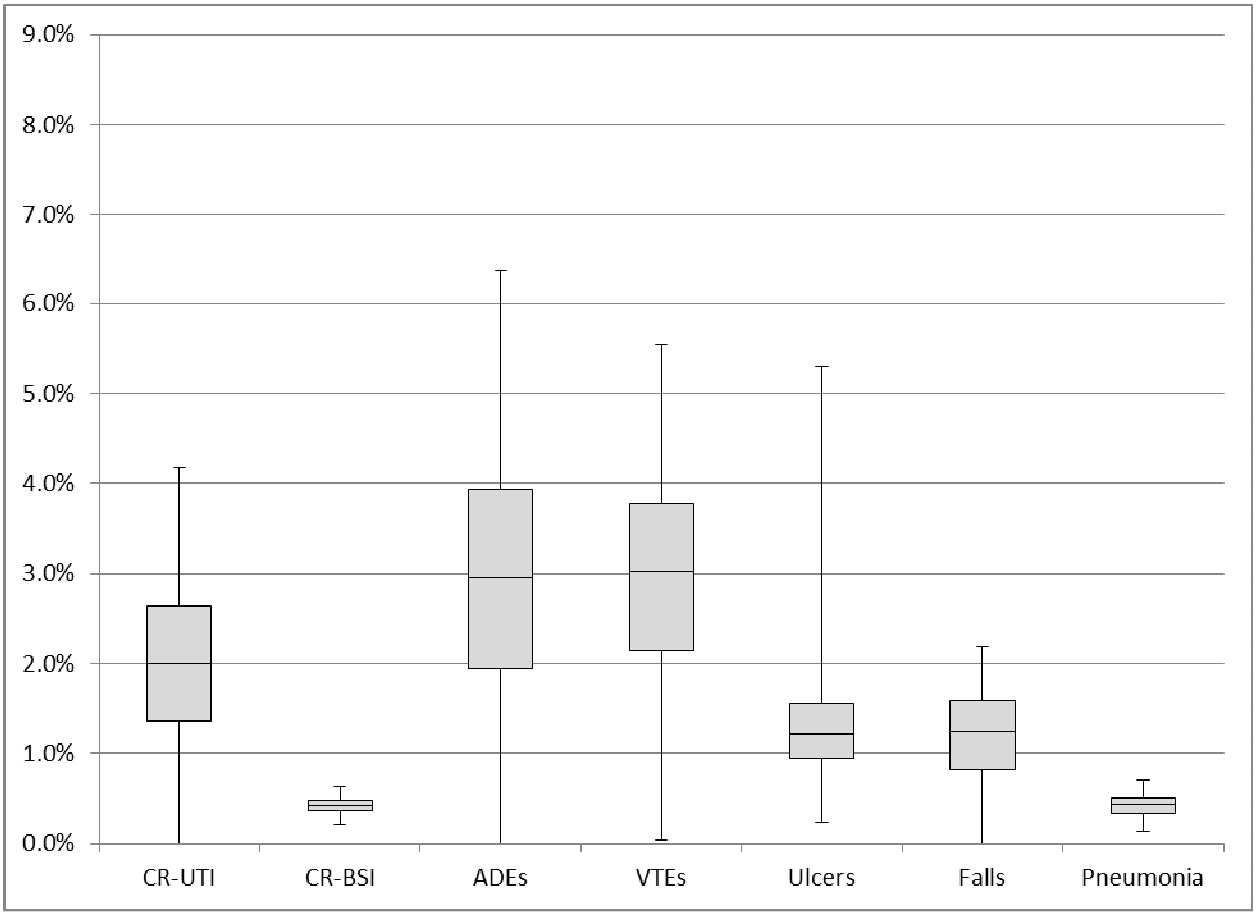
Incidence Rates

To begin our calculation of incidence and/or prevalence rates for each adverse event, we gathered information regarding total number of hospitalizations for both HICs and LMICs. We calculated the range of total hospitalizations for HICs to be between 94.3 million (M) and 143.4 M. The total number of hospitalizations for LMICs was estimated between 121.9 M and 312.2 M.

The first major challenge was to estimate the number of people who were affected by these adverse events. The incidence rate was defined as the number of new cases per population in a given time period. The prevalence rate was defined as the number of cases of a given disease in a specified population at a designated time.[1] In cases in which only incidence or only prevalence

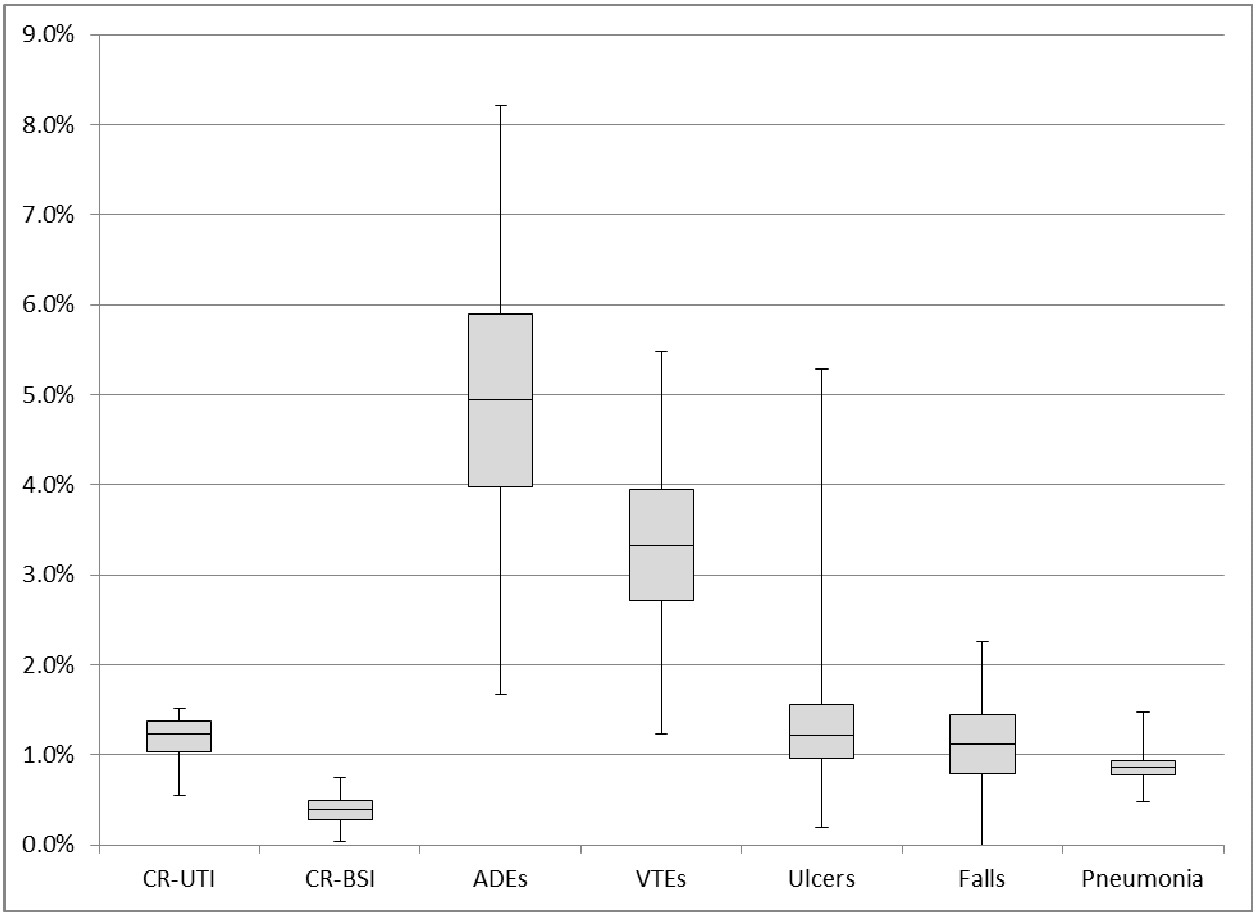
was available, we estimated the missing parameter using the relationship: prevalence = incidence x duration. Since no population-level estimates were available, we created them by multiplying the rates of adverse events for hospitalized patients by the number of hospitalizations. That is, if the rate of adverse drug events was 5.0 per 100 hospitalizations, and we estimated that there were 117.8 million hospitalizations in HICs, then we would estimate that there were 5.8 million adverse drug events in HICs (these numbers are approximate because the number of ADEs presented in Table 3 actually come from the Monte Carlo model which presumes a range of hospitalizations and a range of incidence). Our most reliable data stemmed from incidence rates reported by HICs.

Figure 1a. Range of incidences used in modelling for low and middle income countries.



CR-UTI is catheter-related urinary tract infections; CR-BSI is catheter-related blood stream infections; ADE is adverse drug events; VTEs is venous thrombo-embolism; Ulcers is decubitous ulcers; Falls is hospital-acquired falls; and Pneumonia is hospital-acquired pneumonia.

Figure 1b. Range of incidences used in modeling for high income countries.



CR-UTI is catheter-related urinary tract infections; CR-BSI is catheter-related blood stream infections; ADE is adverse drug events; VTEs is venous thrombo-embolism; Ulcers is decubitous ulcers; Falls is hospital-acquired falls; and Pneumonia is hospital-acquired pneumonia.

Below is a case definition and a detailed description of the search and results for each of the seven adverse events of interest in this study:

1. Adverse Drug Events

Adverse drug events (ADEs) are noxious, unintended, and undesired events that occur as a result of an error at any point in the process of administrating a medication, including ordering, transcribing, dispensing, and administering medications.[2] Patients who experience these events may suffer from injury or death as a result of the error,[3] and the costs to treat these patients are substantial due to longer lengths of stays and increased treatment.[4] To calculate the health and financial burden of ADEs, our literature review excluded studies in which ADEs were either the primary diagnosis for hospitalization, occurred in the outpatient setting, focused only on rates of drug-specific ADEs, or occurred due to patient noncompliance.

The primary search resulted in 508 publications from years 1980-2010. Thirty of the 508 publications were from low-income countries. To ensure all publications for low-income countries were captured, new searches specific to these countries were then carried out. These searches resulted in an additional 193 articles. The articles from which we drew incidence rates are reported in Table 7.

2. Hospital-Acquired Infections (HAIs)

a. Nosocomial Pneumonia

Nosocomial pneumonia (NP) or hospital-acquired pneumonia is defined as pneumonia occurring more than 48 hours after hospital admission and excluding any infection that is incubating at the

time of hospital admission.[5] Most patients with nosocomial pneumonia are those with severe underlying disease, immune suppression, depressed sensorium, and cardiopulmonary disease, and those who have had thoraco-abdominal surgery.[6] The major causative organism for the disease is aerobic Gram-negative bacilli, particularly Pseudomonas Aeruginosa.[7]

The primary literature search produced 1,318 articles, of which 133 were from low-income countries. Supplemental searches were carried out, which produced approximately 2,000 additional articles. We hand-sifted through these abstracts and included any that provided relevant inputs for the modeling (e.g. incidence rates) that we employed for this project..

b. Catheter-related Blood Steam Infections

A catheter-related blood stream infection (CR-BSI) is defined as bacteremia or fungemia in a patient who has an intravascular device and one or more positive blood culture samples obtained from a peripheral vein, has clinical manifestations of infection (such as fever, chills, and/or hypotension), and has no apparent source for bloodstream infection (other than the central venous catheter). In addition, one of the following should be present: (1) a positive result of semi-quantitative (15 colony forming units [CFU] per catheter segment) or quantitative (10^2 CFU per catheter segment) CVC culture, whereby the same organism is isolated from a CVC segment and a peripheral blood sample; (2) simultaneous quantitative cultures of blood samples with a ratio of not less than 5:1 (CVC versus peripheral); and (3) differential time to positivity (positive blood culture occurs at least 2 hours earlier in the sample from the CVC than in the peripheral blood).[8]

The literature search located 280 articles. Of these, 19 were from low-income countries and 254 were after the year 1995.

c. Catheter-related Urinary Tract Infections

A catheter-related urinary tract infection (CR-UTI) in patients with indwelling urethral catheters, indwelling suprapubic catheters, or undergoing intermittent catheterization is defined by the presence of symptoms or signs compatible with UTI with no other identified source of infection along with greater than or equal to 10^3 colony-forming units per milliliter of greater than or equal to 1 bacterial species in a single catheter urine specimen or in a midstream voided urine specimen from a patient whose urethral, suprapubic, or condom catheter has been removed within the previous 48 hours.[9]

The primary search for Urinary Tract Infections resulted in 212 articles. Of these, 108 were published after 1995 and 22 were from LMICs. Supplemental searches found an additional 275 articles.

3. Venous Thrombo-embolisms

Venous thrombo-embolism (VTE) is a disease that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). It results in long-term complications including chronic thrombo-embolic pulmonary hypertension (CTPH) and the post-thrombotic syndrome (PTS). Venous thrombo-embolism results from a combination of hereditary and acquired risk factors, also known as thrombophilia or hyper-coagulable states. Vessel wall damage, venous stasis, and increased activation of clotting factors are the fundamental basis for thrombosis. Deep vein

thrombosis commonly presents with pain, erythema, tenderness, and swelling of the affected limb.[10]

The primary literature search produced 8,383 articles. Additional searches were carried out to identify additional sources, and produced over 2,000 additional publications. The majority of these secondary searches focused on low-income countries. We hand-sifted through the abstracts of these publications, yielding a total of 442 studies that appeared to provide relevant data to consider for this project To calculate the health and financial burden of VTEs, our literature review excluded studies in which VTEs were the primary diagnosis for hospitalization

4. Falls in the Hospital

An inpatient fall is defined as an unintentional descent to the floor or ground in a conscious patient.[11] Our literature review specifically focuses on falls that occur in the hospital while a patient is hospitalized for a medical or surgical condition.

Many articles examined falls in general, and were not exclusive to the inpatient setting. The primary search found 188 articles, of which only 1 article was from a low-income country. Further searches were carried out to expand the breadth of articles. However, due to the dearth of publications in this area, we were able to locate less than 200 additional articles, many lacking merit or published solely in foreign languages.

5. Decubitus Ulcers

A decubitus ulcer is a defect in the skin that may extend through the subcutaneous layer into the underlying fascia. It results from necrosis of tissue caused by vascular occlusion, which occurs when the skin is pressed against a firm surface and has a bony prominence, or when vessels are deformed and collapse.[12] Susceptibility to pressure ulcers comes from a combination of external factors (pressure, friction, shear force, and moisture), and internal factors (e.g. fever, malnutrition, anaemia, and endothelial dysfunction).[13] Patients undergoing surgery are prone to develop pressure ulcers during the surgical procedure.[14]

The primary literature search produced 206 articles. Secondary searches produced over 500 more articles but few of these contributed additional information after we hand-sifted through the abstracts.

The Global Burden of Disease Model

The key inputs for the GBD model are discussed in this section. These data were used to project the number of people affected (both short-term and long-term), the clinical outcomes (e.g. proportion of affected population who fully recover, have short-term disability, long-term disability, or die due to unsafe care), life expectancy, and Disability-Adjusted Life Years (DALYs).

Disability–Adjusted Life Years (DALYs)

For each condition, we established a methodology for calculating the Disability-Adjusted Life Years (DALYs) lost due to each of the seven adverse events identified above. We established these estimates separately for HICs and LMICs. This model follows standard calculation for

DALYs. For each condition, the data collection included the following outcomes, following standard Global Burden definitions when possible:[1]

- Hospitalization Rates: Hospitalization rates are defined as the number of age-standardized acute-care admissions per 100,000 citizens per year.
- Incidence Rates: Incidence rates are defined as the number of new cases per population per year.
- Age of Occurrence: The age of occurrence is defined as the mean age at which a disease or condition is first diagnosed.
- Duration of Disease or Condition: The duration of disease or condition is defined as the mean number of years following diagnosis during which the disease or condition (i.e. sequela of the injury) is present.
- Disability Weight: The disability weight places a value on the extent of the disability associated with the years of life with the disability (ranges from zero – perfect health – to one – death).
- Clinical Outcomes:
    - Injuries leading to full recovery: Injuries where there is no residual disability by the time of hospital discharge.
    - Injuries leading to short-term disability: Injuries for which there is residual disability following hospital discharge, but no residual disability at one year.
    - Injuries leading to long-term disability: Injuries for which there is residual disability at one year, which may range from mild to severe

- Injuries leading to mortality: Injuries leading to mortality were defined as injuries resulting directly or indirectly in a case fatality during or after the initial hospitalization.

Calculated Parameters

Another key parameter is life expectancy, which is necessary to calculate L_{death} (see model below). Following convention in the calculation of DALYs, we used 81.3 as the value for life expectancy, based on model life-table West Level 26, which has a life expectancy at birth of 82.5 for females and 80.1 for males.[15] After estimating the numbers of hospitalizations that occur, we multiplied these data with our incidence (or prevalence) data on the number of patients injured within each adverse event, giving us population-level estimates for number of adverse events in HICs and LMICs.

We also used these data to estimate the age at which the adverse event occurred, again making these estimates separately for HICs versus LMICs whenever possible. Here, the individual studies varied in terms of the age at which the adverse event occurred and the specific type of adverse event. We identified a range of ages for each type of adverse event and input those ranges into the Monte Carlo model (see below) to calculate a best estimate for age for each type of adverse event, separately for HICs versus LMICs.

We estimated, based on the literature, the proportion of patients who had an adverse event who fell into each category of clinical outcomes (e.g., no substantial disability, short-term disability, long-term disability, and death, see Table 4). In many, though not all, of the studies, the clinical sequelae (the proportion that died or had long-term injury, for instance) was reported. We used

those reports to make estimates of how often patients are injured or killed due to adverse events. When data were not available from LMICs, we used data on the clinical sequelae from HICs.

Next, we used the literature to define the duration of the injury. Again, the duration varied across studies and across adverse events. We generally found good data on duration of injury from studies in high income countries but poor data on duration of injury from low income countries. We used a range of duration for short-term disability. When ranges were not available, we assumed that the range was 20% higher or 20% lower than the estimates from the literature. We also assumed (due to a lack of data) that the duration of short-term injuries was the same in the LMICs as that for HICs (see Table 5). These data were used in the Monte Carlo model.

We used the WHO GBD reports to identify disability weights for each type of adverse event.[1] There were very few adverse events for which we had a direct disability weight available, although for nearly every type of adverse event, we were able to find a clinically analogous condition for which WHO had created a disability weight (see Table 6). We defined a condition as "clinically analogous" if it generally affected the same organ system and cause a similar level of disability or death. We recognize, however, that the lack of an exact match between our adverse events of interest and the current disability weight classification scheme is a limitation. The models included the number of people at risk, rate of hospitalization, average age at the time of acquiring the condition, four clinical outcomes (1) death, 2) short-term disability followed by long-term disability, 3) short-term disability then full recovery, and 4) no or minimal disability), duration of the condition, average direct costs related to care of condition per episode, and disability weights. For each condition, it is necessary to have a disability weight to place a value

on the extent of the disability associated with the years of life with disability. By definition, the disability weight will range from zero (perfect health) to one (death).[16]

The distribution of the incidence rates are outlined above and the distributions of other key input variables are shown in tables below.

Disability-adjusted life years model

DALYs are a measure of health gaps – the difference between actual life years lived and those that would have been lived in a state of full health. As such, DALYs are a negative measure – an indicator of the gap between actual health and potential health that results from disability and premature death. Calculating DALYs due to a specific condition therefore involves aggregating the Years of Life Lost (YLL) due to premature death and the Years of Life with Disability (YLD).

The formula for YLL is:

$$N * \left\{ \frac{KCe^{ra}}{(r+\beta)^2} * \left\{ e^{-(r+\beta)(L+a)}[-(r+\beta)(L+a)-1] - e^{-(r+\beta)a}[-(r+\beta)a-1] \right\} + \frac{1-K}{r} * (1-e^{-rL}) \right\}$$

Where:

K = age weighting modulation factor (set at 1)

C = constant (0.1658)

r = the discount rate (0.03)

a = the age of death

β = parameter from age weighting function (0.04)

L = life expectancy at age a

N = the number of people living affected by the condition

And the formula for YLD is similar, with the addition of the disability weight for the specific condition (D): [16]

$$N * D\left\{\frac{KCe^{ra}}{(r+\beta)^2} * \left\{e^{-(r+\beta)(L+a)}[-(r+\beta)(L+a)-1] - e^{-(r+\beta)a}[-(r+\beta)a-1]\right\} + \frac{1-K}{r} * (1-e^{-rL})\right\}$$

Where the variables are as above, except:

L = duration of disability

a = the age at which the disability begins

D = the disability weight for that particular condition.

Table 2. Mean age at acquiring condition, by level of income

	Low- and Middle-Income			High-Income		
	Best Estimate	Low Estimate	High Estimate	Best Estimate	Low Estimate	High Estimate
Catheter-related UTI	65	59	72	75	68	81
Adverse drug event	49	44	54	65	59	72
Falls	54	49	60	70	63	77
Catheter-related blood stream infections	55	50	61	55	50	61
Nosocomial pneumonia	53	48	58	60	54	66
Decubitus ulcers	54	49	60	62	56	68
Venous thrombo-embolism	41	37	45	60	54	66

Table 3. Disability weights associated with adverse events

	Short-term Disability			Long-term Disability		
	Disability	High	Low	Disability	High	Low

	Weight	end	end	Weight	end	end
Catheter-related UTI	0.05	0.06	0.04	0.1	0.12	0.08
Adverse drug event	0.05	0.06	0.04	0.05	0.06	0.04
Falls	0.05	0.06	0.04	0.27	0.324	0.216
Catheter-related blood stream infections	0.2	0.24	0.16	0.2	0.24	0.16
Nosocomial pneumonia	0.28	0.336	0.224	0.1	0.12	0.08
Decubitus ulcers	0.07	0.084	0.056	0.1	0.12	0.08
Venous thrombo-embolism	0.1	0.12	0.08	0.1	0.12	0.08

Table 4. Clinical outcomes of adverse events (%)

	Low- and Middle-Income				**High-Income**			
	No injury	Long-term disability	Mortality	Short-term disability	No injury	Long-term disability	Mortality	Short-term disability
Catheter-related UTI	0.0%	0.0%	6.0%	94.0%	0.0%	2.0%	2.0%	96.0%
Adverse drug event	0.0%	2.9%	1.3%	95.8%	0.0%	6.0%	1.1%	92.9%
Falls	65.0%	1.4%	0.15%	33.5%	65.0%	1.4%	0.15%	33.5%
Catheter-related blood stream infections	0.0%	5.0%	18.0%	77.0%	0.0%	5.0%	18.0%	77.0%
Nosocomial pneumonia	0.0%	5.0%	20.0%	75.0%	0.0%	5.0%	20.0%	75.0%
Decubitus ulcers	0.0%	6.0%	0.5%	93.5%	0.0%	6.0%	0.5%	93.5%
Venous thrombo-embolism	0.0%	20.0%	3.0%	77.0%	0.0%	20.0%	3.0%	77.0%

Table 5. Duration of disability (best estimate, range), in years

	All Countries
	Duration of injury in years
Catheter-related UTI	0.1 (0.08, 0.12)
Adverse drug event	0.2 (0.16, 0.28)
Falls	0.5 (0.4, 0.6)
Catheter-related blood stream infections	0.4 (0.32, 0.48)
Nosocomial pneumonia	0.2 (0.16, 0.24)
Decubitus ulcers	0.5 (0.4, 0.6)
Venous thrombo-embolism	0.8 (0.64, 0.96)

Table 6. Clinically Analogous Conditions (Proxies) Used To Estimate Disability Weights

	Short-term Disability	Long-term Disability
	Disability Weight	Disability Weight
Catheter-related UTI	0.05	0.1
PROXY: Nephritis (Acute)	**0.107**	**0.107**
Adverse Drug Event	0.05	0.05
PROXY: Multiple potential complications including renal failure, liver failure, etc.)	**Range from 0.05 to 0.2**	**Range from 0.05 to 0.2**
Falls	0.05	0.27
PROXY: Sprains (Short-term), Femur fracture (long-term)	**0.067 (sprains)**	**0.272**
Catheter-related blood stream infections	0.2	0.2
PROXY: Endocarditis	**0.17 to 0.32**	**0.17 to 0.32**
Pneumonia	0.28	0.1
PROXY: Lower Respiratory Infections	**0.28**	**0.099**
Decubitus Ulcers	0.07	0.1
PROXY: Open Wound	**0.108**	**0.108**
Venous Thrombo-embolism including pulmonary embolism	0.1	0.1
PROXY: COPD symptomatic cases	**0.19 to 0.42**	**0.19 to 0.42**

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Table 7. Primary Data Sources for Estimating Incidence Inputs for Adverse Events, low-income (LMICs) and high-income (HICs) countries.

HOSPITAL ACQUIRED INFECTIONS (HAIs) **Cather-Related Blood Stream Infections (BSI)**	
AUTHOR LAST NAME (YEAR)	**REPORTED INCIDENCE RATE OF ADVERSE EVENT**
High-income	
US CDC 2009[1]	**0.12%** (ICU and inpatient)
EU 2008 Report[2]	**0.43%**
Klevens 2007[3]	**0.67%**
National Quality Report, AHRQ 2009[4]	**4%** (Medicare beneficiaries FFS with CVC placement)
Pronovost 2006 [5]	**0.62%** (in ICU)
Shorr 2003 [6]	**3.3%** (weighted overall rate of CLBSI based on 61 prospective trials)
Siempos 2009[7]	**1.57%(** in ICU, combination of studies from Mexico, USA, Belgium, Argentina, France, Spain)
The RAISIN Working Group 2009[8]	**0.794%** (French ICU)
Rosenthal 2010[9]	**2.0% (1.9-2.2)**
Vonberg 2006[10]	**0.43%**
Low-income	
Rosenthal 2009[11]	**7.4%** in 18 INICC countries **13.9%** (NICU) **4.4%** (ICU)
Leblebicioglu 2007 [12]	**12.2%** (ICU, Turkey)
Rosenthal 2009[11]	**0.16%-2.31%** (ICU) ; **0.24%-0.60%** (neonatal ICU)
Starling 1997[13]	**0.58%**
Lahsaeizadeh 2008[14]	**1.3%**
Cetin 2005[15]	**0.02%**
Klavs 2003[16]	**0.3%**
Duerink 2006[17]	**0.26%**

Moreno 2006[18]	**5.8%** (ICU)
Jaballah 2007[19]	**5.9%**
Madani 2009[20]	**13.5%**
Inan 2006[21]	**0.969%**
The RAISIN Working Group 2009[8]	**0.327%** (ICU)
Urinary Tract Infections (UTI)	
High-income	
Edwards 2007[22]	**0.31%-0.75%**
Gastmeier 2001[23]	**1.2%**
Bouza 2001[24 25]	**0.7%**
Stamm 1991[26]	**2-4%**
Doyle 2001[27]	**3%**
Vonberg 2006[10]	**0.68%**
Saint 2006[28]	**13.1%** (indwelling catheter) **7.0%** (condom catheter)
Klevens 2007[3]	**424,060 UTIs** in adults and children (not including ICU)
Vonberg 2006[10]	**0.68%**
Low-income	
Rosenthal 2010[9]	**6.3%** (adult ICU) **4.0%** (PICU)
Leblebicioglu 2007 [12]	**8.9%** (ICU)
Starling 1997[13]	**0.9%**
Lahsaeizadeh 2008[14]	**3.7%**
Cetin 2005[15]	**0.25%**
Danchaivijitr 2005[29]	**1.4%**
Klavs 2003[16]	**1.2%**
Leblebicioglu 2003[30]	**1.7%**
Durmaz 2000[31]	**0.41%**

Sujijantararat 2005[32]	**31.68%**
Moreno 2006[18]	**2.5%** (ICU)
Inan 2006[21]	**1.363%**
Pneumonia	
High-income	
Horan 1986[33]	**0.42-0.77%**
Klevens 2007[3]	**0.67%**
Jokinen 1993 [34]	**1.11%**
Almirall 2000 [35]	**0.162%**
American Thoracic Society 1996[36]	**0.5-1.0%**
Low-income	
Klavs 2003[16]	**0.3%**
Starling 1997[13]	**0.65%**
Ellidokuz 2003[37]	**0.25%**
Durmaz 2000[31]	**0.2%**
Alp 2004[38]	**6.8% (ICU patients)**
Mandani 2009[20]	**54.6% of all HAIs were VAP**
Moreno 2006[18]	**4.0% ICU patients (VAP)**
Inan 2006[21]	**20.76 infections/1000 ventilator-days (VAP)**
ADVERSE DRUG EVENTS (ADEs)	
Low-income	
Arulmani 2008[39]	**3.74%**
Baniasadi 2008 [40]	**1.3%**
Benkirane 2009 [41]	**4.24%**
Bhatt 1999[42]	**2.4% – 6.7%** (India)
Jha 2007 [43]	**0.86%**
Jose 2006[44]	**0.15%**

Khan 2005[45]	**0.36%**
Major 1998 [46]	**6.72%**
Mehta 2008[47]	**5.64%**
Pourseyed 2009[48]	**11.75%**
Ramesh 2003[49]	**3.7%**
Uppal 2000[50]	**0.3%**
High-income	
National Quality Report 2009[4]	**3.4%-8.9%**
Classen 1997[51]	**2.43%**
Classen 1991[52]	**1.67%**
Bates 1995[53]	**6.5%**
Bates 1999[54]	**0.147%** ADEs (before CPOE) **0.096%-0.149%** (after CPOE)
Bates 2003[55]	**0.66%** (Brigham and Women's Hospital) **3.33%** (Wishard Memorial Hospital)
Gurwitz 2003[56]	**5.01%**
Hallas 1992[57]	**11.4%** (prevalence)
Hanlon 2006[58]	**0.192%**
Holdsworth 2007[59]	**6.3%** (before CPOE) **3.1%** (after CPOE)
Jha 1998[60]	**14.2%**
Lazarou 1998[61]	**6.7%**
Miller 2006 [62]	**10.4%** (reported ADE to GP in past 6 months)
Pirmohamed 2004[63]	6.5% (1225 out of 18,820) of admissions related to ADR
Schmader 2004[64]	**0.20%** (geriatric inpatient unit) **0.19%** (general inpatient unit) **0.20%** (geriatric outpatient clinic) **0.20%** (general outpatient clinic)
Runciman 2003[65]	**26%** of hospital related incidents were medication related

Thomas 2000[66]	**2.9%**
Thomsen 2007[67]	**14.9%** (4.0%-91.3%)
Van de Hooft 2008[68]	**3.5%** (122 of 3515 of all admissions were classified as ADR related)
Bates 1995[69]	**1.47%**
Baker 2004[70]	**7.5%**
FALLS IN HOSPITAL	
Low income	
An 2009[71]	**1.2%** of patients had fallen in hospital
Peden 2002[72]	WHO estimates that in 2000, 283,000 people died as the result of falls, globally
High-income	
Bates 1995[73]	**0.66%**
Fischer ID 2005[74]	**0.31%**
Halfron 2001[75]	**0.24%**
Hitcho 2004[76]	**0.38%**
Izumi 2002[77]	**12.5%**
Krueger 2001[78]	**52.8%**
Morgan 1985 [79]	**2.0%**
Nakai 2006[80]	**1.3%**
Healey 2008[81]	**0.3%-1.4%**
Mahoney 1998[82]	**2%**
Oliver 2006[83]	**0.4%–1.4%**
Halfon 2001 [75]	**0.22%**
Morgan 1985[79]	**1.87%**
Hitcho 2004[76]	**0.338%**
Nakai 2006 [80]	**1.3%**
Schwendimann 2006 [84]	**7.2%**
Schwendimann 2006[85]	**12.2%**

Tan 2005[86]	**0.132%**
Vassallo 2005[87]	**18.2%**
Webster 2010[88]	**9.2%** (prevalence)
VENOUS THROMBO-EMBOLISMS (VTE)	
Low-income	
Agarwal 2009 [89]	**34%**
Atichartakarn 1988[90]	**4%**
Baeshko 1999[91]	**33.6%**
Bagaria 2006 [92]	**6.12%**
Darze 2005[93]	**9.1%**
Dhillon 1996[94]	**62.5%**
Diogo-Filho 2009[95]	**1.7%**
Jain 2004[96]	**4.4%**
Leizorovicz 2005 [97]	**0.2% to 1.2%**
Osime 1978[98]	**30%** (men, post-surgery) **70%** (women, post-surgery)
Pandley 2009[99]	**0.01746%**
Piovella 2005 [100]	**41.0%**
Phornphibulaya 1984[101]	**12.2%**
Prasannan 2005[102]	**57%** of surgeons reported VTE-related morbidity
High-income	
Caprini 2003 [103]	**5% -20%** (with adequate thromboprophylaxis after THRS) **50%** (in the absence of thromboprophylaxis after THRS)
Cushman 2004[104]	**0.192%**
Geerts 2003[105]	**13-31%** (critical care patients without prophylaxis)
Geerts 2001 [106]	**25%** (after general surgery without prophylaxis)
Geerts 2004[107]	**10%-40%** (medical or general surgical patients) **40 to 60%** (following major orthopedic surgery)

Hansson 1997[108]	**0.138%**
Meyer 1995[109]	**6%-9%**
Oger 2000[110]	**0.183%**
Prandoni 1996[111]	**4.9%** after 3months **8.6%** after 6 months **17.5%** after 2 years **24.6%** after 5 years **30.0%** after 8years
Robinson 1997[112]	**2.5% (**asymptomatic prox DVT)
Rosencher 2005[113]	**1.34%** (symptomatic VTE at 3mos)
Samama 1999[114]	**15%** (medical patients without prophylaxis)
White 2003[115]	**0.8%**
DECUBITUS ULCERS	
Low-income	
Bork 2007[116]	1% of all hospital discharges (25% of which were present upon admission)
Chauhan 2005 [117]	**4.94 %**
Fu 1998[118]	**1.63 %**
Karadag 2006[119]	**54.8%**
Leblebici 2007[120]	**1.6%**
Manley 1978[121]	**4.5%** (prevalence)
Sayar 2009[122]	**14.3%**
Sae-Sia 2005 [123]	**47%**
Suriadi 2008 [124]	**7-29%** (international)
Kwong 2005[125]	**2.1%-31.3%**
Srisupan 2005 [126]	**5.76 – 10.8%**
Uzun 2007 [127]	**9.9%**
High-income	
Allman 1995[128]	**12.9%**

Bennett 1989[129]	412,000 patients in UK annually (7.95 million inpatients at risk annually)
Kaltenthaler 2001[130 131]	**4.7%-32.1%**
Frantz 2004[132]	**7%-38% (**based on studies from the late 1990s)
Graves 2005[133]	Mean number of cases per region = 95,910 (8 regions)
Hengstermann 2007[134]	**16.7%** (prevalence, geriatric patients)
Muurinen 2009[135]	**15.1%** (prevalence, nursing home residents) **22.1%** (prevalence, long-term care hospitals)
Lahmann 2012[136]	**10.1%**
Lahmann 2005[137]	**16.8 %**
Lindgren 2004 [138]	**11.7%**
Lindholm 2008[139]	**16%**
Takahashi 2008[140]	**14.8%** (prevalence)
Tannen 2008 [141]	**18.1 – 28.8 %** (German hospital patient) **28.1 – 41.1 %** (Dutch hospital patients)
Thomas 1996[142]	**12.9%** (prevalence of Stage 2 or greater pressure ulcers)
Thomas 2001[143]	**0.017%**
Vanderwee 2007[144]	**18.1%** (prevalence in hospital convenience samples)
Wann-Hansson 2008[145]	**13.2 %**
Whittington 2004[146]	**7%-9%**
Lahmann 2005[147]	**11.7%** (prevalence)
Bours 2002[148]	**23.1%** (prevalence)
Wilborn D 2006[149]	**8.3-15.3%** (prevalence in hospitals and nursing homes)

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