Burden of healthcare-associated infections in Italy: incidence, attributable mortality and disability-adjusted life years (DALYs) from a nationwide study, 2016

Burden of Healthcare-Associated Infections in Italy: incidence, attributable mortality and Disability-Adjusted Life Years (DALYs) from a nationwide study, 2016.

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Abstract

Background: Healthcare-associated infections (HAIs) are an increasing public health threat. Measuring disease burden in disability adjusted life-years (DALYs) allows to combine morbidity and mortality in one figure, as it represents the summation of years lived with disability and years of life lost.

Aim: To evaluate the incidence, attributable deaths and burden of the most significant HAIs in Italy.

Methods: Prevalence data from the study sample of the 2016 national national Point Prevalence Survey of HAIs in acute-care settings were used to estimate the incidence of five HAIs. The methodology from the Burden of Communicable Diseases in Europe (BCoDE)-project was employed for DALY calculations, adapting the disease models to the Italian population.

Findings: We estimated a total of 643,620.11 (95% uncertainty interval, UI 615,796.77 – 671,144.41) new yearly cases of HAIs and 29,437.58 (95% UI 27,338.47 – 31,848.93) deaths in Italy in 2016. The total annual DALYs were estimated to be 426 427.54 (95% UI 376,030.94 – 479,478.14), corresponding to 702.53 DALYs (95% UI 575.22 – 844.66) per 100,000 general population. HA BSI accounted for the majority of total DALYs (59%), HAP for 29%, SSI for 9%, CDI for 2% and UTI accounted for less than 1% of total DALYs.

Conclusion: Results of this study suggest HAIs have a substantial burden in Italy. Reducing the burden of HAIs through infection prevention and control efforts is an achievable goal. This study provides data that could be used to guide policy-makers in the implementation of these measures.

keywords: Daly; Burden; Healthcare Associated Infections; Italy;

Introduction

Healthcare associated infections (HAIs) represent a significant threat to patient safety and are recognized as a metric for quality of healthcare. [1] Even though up to 70% of HAIs are estimated to be preventable, [1] and several interventions have proven effective in reducing the burden of HAIs, [2] HAIs and antimicrobial resistance (AMR) remain a serious public health issue in Italy. [3] The most recent Italian Point Prevalence Survey (PPS) of HAIs in acute-care settings, conducted in 2016 as part of the European Center for Disease Prevention and Control (ECDC) survey of HAIs in the European Union (EU) and in the European Economic Area (EEA), found the prevalence of patients with at least one HAI was 8.0%. [4] This number was higher than the EU/EEA prevalence in 2016-2017 (5.9%) and increased since 2011, when the first Italian survey found a prevalence of 6.3%. [5, 6]

In order to evaluate the potential benefit of infection prevention and control (IPC) interventions, an assessment of the burden of disease is required. The disability adjusted life-year (DALY) is a health metric that combines morbidity and mortality of a disease in one figure, as it represents the summation of years lived with disability and years of life lost. [7] Expressing disease burdens in DALYs allows to compare different diseases, both communicable and non-communicable, and is therefore a useful tool for evidence-based healthcare policy prioritization. [8]

The ECDC estimated, using 2011-2012 EU/EEA PPS data and applying the methodology of the Burden of Communicable Diseases in Europe (BCoDE) project, [9] the burden of the six main types of HAI: healthcare associated pneumonia (HAP), urinary tract infection (HA UTI), *Clostridium difficile* infection (HA CDI), neonatal sepsis (HA NS), primary bloodstream infection (HA BSI) and surgical site infection (SSI). [10] In this study, the same methodology was used to evaluate the burden of the most significant HAIs in Italy, based on data from the 2016 national PPS. The purpose of the study was to evaluate the incidence, number of deaths and DALYs attributable to the

five most significant HAIs in Italy. We believe this comprehensive approach to evaluating the burden of HAIs will be useful to inform policymakers, providing evidence to support investing in IPC interventions.

Methods

Data collection

Data from the representative sample of the second Italian PPS, conducted in 2016 as part of the ECDC PPS, were used for this study. The representative sample consisted of 14,773 patients from 56 hospitals. The applied definitions, methodology for data collection and sampling procedure were previously described. [11] Briefly, demographic and clinical data were collected for each patient included in the survey. Patients were stratified according to the severity of underlying medical conditions according to the Mc Cabe score. [12] If the patient was affected by a HAI on the day of the survey, further data including the type of HAI and date of onset were collected.

The approval of at least one Local Health Unit's Ethics Committee per Italian region participating in the PPS was obtained to conduct the survey and analyze data. As all collected data were anonymized, the informed consent of patients was not required.

Outcome measure

The DALY measures health gaps as opposed to health expectancies. It measures the difference between a current situation and an ideal situation where everyone lives up to the age of the standard life expectancy, and in perfect health. The DALY combines in one measure the time lived with disability and the time lost due to premature mortality:

DALY = YLL + YLD

Where: YLL: years of life lost due to premature mortality, YLD: years lived with disability.

The YLL metric essentially corresponds to the number of deaths multiplied by the standard life expectancy at the age at which death occurs. The basic formula for calculating YLLs for a given cause, age or sex, is:

YLL = N x L

where: N: number of deaths, L: standard life expectancy at age of death (in years).

To estimate YLDs on a population basis, the number of disability cases is multiplied by the average duration of the disease and a weight factor that reflects the severity of the disease on a scale from 0 (perfect health) to 1 (death). The basic formula for one disabling event is:

YLD = I x DW x L

where: YLD: years lived with disability, I: number of incident cases, DW: disability weight, L: average duration of disability (years). [13, 14]

Data Processing

Using prevalence data from the study sample of the 2016 national PPS, the sex- and age- specific incidence of five HAIs was estimated: healthcare-associated pneumonia (HAP), HA-urinary tract infections (HA UTI), HA-bloodstream infections (HA BSI) excluding neonatal-BSI, surgical site infections (SSI), HA-*Clostridium difficile* infections (HA CDI). HAIs were defined according to EU case definitions. [12] In this study, a syndrome-based approach was used, with the exception of HA CDI. Incidence was interpolated using the Rhame and Sudderth formula. [15] In order to model the disease course and calculate DALYs, we followed the methodology from the Burden of Communicable Diseases in Europe (BCoDE)-project, adapting the disease models to the Italian population, stratified according to the McCabe score. [12]

DALY calculation

Step 1: Estimation of HAI prevalence

Data on the prevalence of each studied HAI in the Italian PPS representative sample was extrapolated for each age, gender and McCabe score stratum.

Step 2: Converting prevalence into incidence

HAI incidence in the Italian PPS study sample was estimated using the Rhame and Sudderth formula: [15]

I=PXLA/LN-INT

where I: rate of new patients with HAIs per 100 admissions, P: percentage of patients with an HAI on the day of the PPS, LA: length of stay of all hospitalized patients (irrespective of the presence of an HAI), LN: length of stay of patients with an HAI, INT: length of stay before HAI onset, LN-INT: length of stay of patients with HAIs from HAI onset until discharge, derived from the median number of days from HAI onset until day of PPS data collection.

Step 3: Extrapolating HAI incidence from the PPS sample to the Italian hospitalized population

Using publicly available data from the Italian Ministry of Health, we extracted the total number of acute-care hospital discharges in Italy of 2016. [16] We then applied the age and sex distribution of the patients in the PPS sample the 2016 acute-care hospital discharges in Italy. Using the same procedure, we applied the Italian PPS sample's McCabe score proportion to the Italian 2016 hospitalized population, thus adjusting for life expectancy; this score is used as a subjective score of underlying illness severity. This simple method of classifying patients according to a prognosis of rapidly fatal (<1 year), ultimately fatal (1–4 years) and non-fatal (>5 years) disease has been shown to be a better predictor of survival than the APACHE II score. [17]

Step 4: Creating disease models using the BCoDE Toolkit v20.0

We used the 20.0 version (the latest available update at the time of submission) of the BCoDE Toolkit to build the Italian models for each of the five HAIs. [9] The toolkit allows the user to personalize the outcome trees of each selected communicable disease. Using the procedure described by Cassini *et al* we created 3 models for each type of HAI, one for each McCabe Score stratum, indicating the median life expectancy (0.5 years, 3 years, >5 years) on the basis of underlying health conditions. [10] Italian National Institute of Statistics (ISTAT) data on the 2016 Italian population and life expectancy were used to populate the models. [18] We employed the same disease models described by Cassini *et al*, [10] applying them to the Italian population.

The age-, gender- and McCabe-specific incidence data for each model, including uncertainty intervals, were incorporated in the calculations as uniform (two variables) or Project Evaluation and Reviewed Techniques (PERT) distributions. [19] Inputted data are available in S1-supplementary-material. The models were then run at 10,000 iterations of the Monte Carlo simulations.

Step 5: output

For each type of HAI, the output included: annual number of HAIs, incidence, number of attributable deaths, and DALYs per case, as well as the number and rate per 100,000 population of DALYs, YLLs and YLDs. For each output, the median and the 95% uncertainty interval (UI) based on the input uncertainties were calculated.

Results

Based on 2016 Italian PPS data, we estimated a total of 643,620.11 new cases (95% UI 615,796.77 – 671,144.41) for the five types of HAI under study. According to our models, 29,437.58 (95% UI 27,338.47 – 31,848.93) deaths were attributable to the five considered HAIs in Italy in 2016. The

total annual DALYs for the five HAIs were estimated to be 426,427.54 (95% UI 376,030.94 – 479,478.14), consisting of 339,767.09 YLL (95% UI 296,268.94 – 384,511.86) and 86,589.03 YLD (95% UI 76,712.53 – 97,577.09), and corresponding to 702.53 DALYs (95% UI 575.22 – 844.66) per 100,000 general population.

Burden estimates per HAI type and Mc Cabe score in terms of incidence, attributable mortality, DALYs, YLLs and YLDs are reported in Table I. The McCabe 1 groups were the most represented for each of the five HAIs in terms of DALYs, mainly due to the high number of HAIs occurring in these patients and to their longer life expectancy. BSI in the McCabe score 1 group had the highest burden (388.08 DALYs per 100,000; 95% UI 314.16 – 467.56), followed by HAP (187.64 DALYs per 100,000; 95% UI 159.24 – 220.88), and SSI (55.49 DALYs per 100,000; 95% UI 47.98 – 63.22). Detailed and aggregated burden data are available in S2-supplementary-material.

Figure 1 shows the disease burden of each HAI, measured in DALYs per 100,000. HA BSI accounted for the majority of total DALYs (59%), HAP for 29%, SSI for 9%, CDI for 2% and UTI accounted for less than 1% of total DALYs. BSI and HAP had the highest burden of disease with respectively 253,119.32 (95% UI 204,650.35 – 305,743.66) and 125,607.35 (95% UI 106,778.19 – 147,607.37) DALYs. BSI had the highest burden in terms of YLLs, while CDI and UTI accounted for a relatively more important disability weight in terms of YLDs but relatively less YLLs. As shown in the Figures 1 and 2, CDI and UTI were associated with a high yearly incidence but a low burden of disease, whereas HAP and BSI accounted for a great amount of DALYs despite a low yearly incidence, due to their high attributable mortality.

Figure 3 shows the overall burden of the five HAIs under study expressed in DALYs per 100,000 general population, per age and gender strata. In total, 56% of DALYs were attributable to men and

44% to women. The age groups with the highest burden were 70-74 for male patients and 45-49 for female patients.

Discussion

HAIs and AMR have been recognized as an increasing public health threat. [20] In Italy, a national action plan to contrast AMR and HAIs was developed in 2017, and several targets for interventions aiming to reduce HAIs and optimize antimicrobial use were defined. [21] Monitoring and evaluating the effectiveness of IPC interventions requires accurate data on the incidence and burden of HAIs. To the best of our knowledge, this is the first study to estimate the burden of HAIs expressed in DALYs in Italy. Results of this study suggest HAIs have a substantial clinical burden in our country, amounting to over 700 DALYs per 100,000 general population based on nationwide data from the 2016 PPS.

The majority of total DALYs were attributable to YLLs (79.7%), indicating mortality is a more important factor compared to long-term sequelae. Concurringly, a recent Greek study found an 80% increase in the daily risk of hospital death within 90 days of admission in patients with an HAI compared to patients without HAI. [22] A higher proportion of total DALYs occurred in men and was greater in the 70-74 years age group. This suggests the burden of HAIs in our country could increase with the ageing population. In our study, BSI and HAP had the highest burden among the considered HAIs (60% and 30% of total DALYs respectively), due in large part to disease severity (4.41 and 1.39 DALYs per case, respectively). Conversely, UTI were associated with a lower burden of disease despite their relatively high incidence (122.81 per 100,000 general population). According to our estimates, the yearly number of cases for the five considered HAIs was of almost 650,000 cases.

Calculating DALYs for the same health conditions across different populations allows to obtain normalized burden estimates, which can highlight setting-specific issues and, particularly in the case of HAIs, can be informative of the quality of healthcare provision in different contexts. Further, quantifying the impact of HAIs in terms of DALYs allows comparisons between different health conditions, and therefore can help inform policy and decisions on how to prioritize resource allocation.

Cassini *et al* used 2011-2012 EU/EEA PPS data to evaluate the burden attributable to six HAIs (the five HAIs analyzed in our study with the addition of neonatal BSI) among participating countries. [10] A total burden of around 500 DALYs per 100,000 general population was found, which is significantly lower than our estimate based on 2016 Italian data, which was obtained using the same approach. HAIs occurring in our country in 2016 would account for 16.34 % of the 2011-2012 EU/EEA DALYs, while the Italian population in 2016 represented 11.9% of the European population. Further research is required to investigate whether the higher burden in our country could be explained by demographic differences of the hospitalized population, epidemiological aspects such as the high incidence of AMR pathogens, [20] less effective preventive strategies, or other factors.

According to the 2009-2013 BCoDE study, [23] the burden of the most significant communicable diseases, including influenza, in the EU/EEA was 260 DALYs per 100,000 general population. Santos *et al* evaluated the burden of diseases and injuries in the EU using data from the 2017 Global Burden of Diseases study. [24] The health conditions that had the highest disease burden in Europe were low back pain, ischaemic heart disease, headache disorders, stroke and neonatal disorders. Results of the study for the considered health conditions in Italy showed low back pain had a burden of 1284 DALYs per 100,000 general population, headache disorders 1110, ischaemic heart disease 749, Diabetes Mellitus 601 and stroke 458. Although comparisons with other health conditions should be interpreted with caution due to methodological differences in the calculations,

results of our study suggest HAIs in Italy have a disease burden similar to that of the highest ranking non-communicable diseases.

A recent study of the burden of coronavirus disease 2019 (COVID-19) in Italy during the first four months of 2020 estimated a total of 121,449 DALYs, consisting of 120 814 YLL and 635 YLD [25]. In comparison, our estimate for the burden of HAIs in 2016 was of just over 400,000 DALYs. Although this would suggest HAIs in 2016 and the first wave of the COVID-19 epidemic in our country were associated with comparable disease burdens, it must be noted that the long-term consequences of COVID-19 are still largely unknown and therefore the burden in terms of YLD could be much more significant.

The COVID-19 pandemic is placing an unprecedented strain on healthcare systems worldwide, [26] although the full extent of its impact on HAI epidemiology is still unclear. IPC resources are understandably being diverted towards outbreak management, which may hinder HAI surveillance and prevention efforts. A number of risk factors for increased HAI transmission are associated with COVID-19, such as the surge in hospital admissions, prolonged hospital and intensive care unit stays and the increase in patients requiring mechanical ventilation. Further, the immune dysregulation associated with severe COVID-19, as well as the use of corticosteroids and immunomodulatory agents for treatment could predispose patients towards developing secondary infections. [27] Another cause for concern is the potential link between COVID-19 and AMR, due to the increasing rates of antibiotic use, sub-optimal prescribing and potential breakdowns in stewardship programs. [28] On the other hand, IPC practices that are essential for controlling the spread of COVID-19 may also contribute in reducing AMR and HAI transmission. Societal focus on COVID-19 has increased awareness of the importance of hand hygiene, environmental decontamination and the use of personal protective equipment. [28]. Improvements in IPC behaviors among at-risk healthcare workers have been reported, and studies conducted one year after SARS outbreaks indicate the ameliorations in hand hygiene and other IPC practices could be

maintained long-term. [29] Further studies will be necessary to determine the effects of these elements on AMR and HAI epidemiology as a consequence of the COVID-19 pandemic.

This study has several limitations. First, there are limitations related to the study design. We assessed the burden of the five most significant HAIs, chosen on the basis of data availability, frequency and feasibility of a personalized model in the BCoDE Toolkit. Therefore, our burden estimates are likely an underestimation, although the five HAIs we considered account for 75% of the total number of HAIs identified by the 2016 Italian PPS. [4] Additionally, we employed a syndrome-based approach for four out of the five HAIs under study, rather than an approach based on the causative pathogen. Infections caused by AMR microorganisms have been associated with a higher burden of disease compared to infections caused by susceptible organisms. [10, 20, 22]

Second, limitations pertaining to the study methodology should be addressed. We employed the Rhame and Sudderth formula to estimate HAI incidence from prevalence data. Even if this method is commonly applied to interpolate incidence from prevalence, its use has been criticized. [10] Further, the outcome trees of the BCoDE toolkit are populated with data from systematic reviews of the literature, which vary in terms of availability, quality and representativeness.

Despite these limitations, this study was based on data collected through the 2016 PPS, which is the most comprehensive and standardized survey conducted on HAIs in acute-care hospitals in our country. Another strength is the adjustment of life expectancy using the McCabe score, which improves the reliability of our estimates.

In conclusion, this nationwide study suggests HAIs had a significant burden of disease in 2016 in Italy. In light of the increasing AMR trends and the ageing Italian population, HAIs are of great concern. Considering a large proportion of HAIs are estimated to be preventable, [1] reducing their burden is an achievable goal. This study provides data which could be used to guide policy-makers in the implementation of measures aiming to reduce the impact of HAIs. The heightened societal

interest towards infectious diseases due to the COVID-19 pandemic could enhance engagement with the threat posed by AMR and HAIs, and the importance of patient safety. Given the concise and clear nature of the DALY metric, our results could help improve public health communication and lead to an increased incorporation of public opinion in health decision-making.

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Conflicts of interest

Declarations of interest: none

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