Excess Mortality and Long-Term Disability from Healthcare-Associated Staphylococcus aureus Infections: A Population-Based Matched Cohort Study

Chiu-Hsia Su1,2, Shan-Chwen Chang3, Jer-Jea Yan2, Shu-Hui Tseng2, Li-Jung Chien2*, Chi-Tai Fang1,3*
1 Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan, 2 Fifth division, Centers for Disease Control, Taipei, Taiwan, 3 Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan

Abstract

Background: Staphylococcus aureus is a leading cause of healthcare-associated infections (HAIs), but the impact of S. aureus HAIs on the long-term survival and functional status of hospitalized patients remain unknown. This study aimed to examine whether S. aureus HAIs increase the risks for long-term mortality and disability.

Methods: We conducted a retrospective population-based matched cohort study of inpatients at 8 medical centers, 43 regional hospitals, and 63 local hospitals which participated in the Taiwan Nosocomial Infection Surveillance (TNIS). We individually matched 3070 patients with S. aureus HAIs to 6140 inpatients without HAIs at a 1:2 ratio by age, gender, hospital, specialty, underlying diseases, and the length of stay before onset of the S. aureus HAI. Main outcome measures are one-year excess risks for mortality, new-onset chronic ventilator dependence, and new-onset dialysis-dependent end-stage renal disease.

Results: We found that patients with S. aureus HAIs had an excess one-year mortality of 20.2% compared with matched uninfected inpatients (P<0.001). The excess risk for new-onset chronic ventilator dependence and dialysis-dependent end-stage renal disease was 7.3% and 2.6%, respectively (Ps<0.001). S. aureus HAIs were also associated with an excess hospital stay of 12 days and an extra cost of $5978 (Ps<0.001).

Conclusion: S. aureus HAIs have substantial negative effect on the long-term outcome of hospitalized patients in terms of both mortality and disability, which should be taken into consideration in future cost-effectiveness studies of the control and prevention interventions for S. aureus HAIs.

Introduction

Staphylococcus aureus is a leading cause of healthcare-associated infections (HAIs) [1,2]. S. aureus infections can cause severe sepsis complicated by acute renal failure and respiratory failure requiring intensive care [3,4]. S. aureus bacteremia is associated with an in-hospital mortality of as high as 15–60% [5], especially in critically ill patients [6–8]. Bacteremia of methicillin-resistant S. aureus (MRSA) [9–13] has a higher attributable mortality than that of methicillin-susceptible S. aureus (MSSA) [2,14]. Thus, S. aureus HAIs can have substantial impacts on the patient’s survival and well-being.

The negative effects of S. aureus HAIs on the outcomes of hospitalized patients have not yet been well studied. The existing literature includes only six small studies, which reported an increased risk for short-term mortality by 2.2–7.3 folds in patients with S. aureus HAIs compared to inpatients without HAIs [15–20]. Most studies focused on surgical site infection (sample size: 18–286 cases) [15–17] or bloodstream infection (sample size: 19 cases) [18]; only one study examined all-type S. aureus HAIs (sample size: 27 cases) [19]. None of the studies have investigated the impact of S. aureus HAIs on mortality beyond 90 days [21]. The functional status of survivors has not been studied, either. The acute respiratory or renal failure occurring during sepsis may be irreversible and thus result in long-term ventilator or dialysis dependence, causing huge financial burdens.

Taiwan Nosocomial Infection Surveillance (TNIS) is a nationwide surveillance system that collects HAI data from more than 100 participating hospitals throughout Taiwan. The TNIS data show that S. aureus is one of the leading causative pathogens of HAIs in Taiwan [22]. MRSA accounts for up to 79% and 81% of all S. aureus isolates at regional hospitals and medical centers, respectively [22]. To understand the impact of S. aureus HAIs on the long-term outcomes of hospitalized patients, we conducted a nationwide population-based matched cohort study of inpatients at 114 hospitals participating in the TNIS.
Methods

Study Design

We conducted a retrospective population-based matched cohort study comparing outcomes between hospitalized patients with S. aureus HAIs and patients without HAIs, matched by age, gender, hospital, specialty, underlying diseases, and the length of stay before onset of the S. aureus HAI. The main outcomes were one-year excess risks for mortality, new-onset chronic ventilator dependence, and new-onset dialysis-dependent end-stage renal disease.

Ethical Statement

To protect the privacy of the patients, the personal identification numbers were encrypted before database linking. The study protocol (no. TwCDCIRB990008) was reviewed and approved a priori by the institutional review board (IRB) of Taiwan Centers for Diseases Control (Taipei, Taiwan). The IRB approved the exemption of informed consent because all personal information had been anonymized.

Settings

Taiwan Centers for Diseases Control established the TNIS in 2006 and invited all hospitals to voluntarily participate. By 2008, 114 out of the total 493 hospitals in Taiwan had joined the TNIS and notified their HAIs cases with registration of the patients’ personal identification (ID) numbers. The 114 hospitals included 6 medical centers, 43 regional hospitals, and 63 local hospitals (with a median bed capacity of 1318, 301, and 182, respectively), which had a total of 3307376 hospitalizations covered by the NHI during the study period from 2006 through 2009.

HAI Surveillance and Notification

In all participating hospitals, infection control nurses routinely review all hospitalizations for all types of HAIs (including bloodstream infection, pneumonia, surgical site infection, urinary tract infection, and other types of HAIs) using the US Centers for Disease Control and Prevention (CDC) (Atlanta, GA, USA) surveillance definitions [23]. The identified HAI cases were notified to the TNIS. The reported data included the patient’s age, gender, HAI onset date, site of infection, and microbiological results (e.g. organisms isolated from blood, urine, respiratory tract, surgical sites, and other non-sterile sites, as well as antimicrobial susceptibility). The onset date was the date when the first clinical symptom(s)/sign(s) occurred or the earliest positive culture was sampled, as specified for the type of HAI by the CDC definition.

Patients with S. aureus HAIs

We included all notified S. aureus HAIs cases that occurred at least 48 hours after admission in 2006–2008 for linkage with the NHI dataset. The flowchart is shown in Figure 1. If a patient had multiple episodes of HAIs during hospitalization, only the first episode and its first isolate were considered in this study. Cases with the HAI occurring within 48 hours of the admission or beyond the hospitalization period were excluded, because we used the length of stay before onset of the S. aureus HAI as one of the matching variables to identify a suitable matched uninfected inpatient [8,14].

Matched Inpatients without HAIs

Each S. aureus HAI case was individually matched at a 1:2 ratio to inpatients without HAIs that were hospitalized during the same study period. The matching was based on age (within a 5-year difference), gender, as well as the same hospital, primary specialty/subspecialty, and indicators of underlying disease severity—including the length of stay before onset of the S. aureus HAI [8,14] and the presence and type of seven classes of severe illnesses at admission (i.e. cancer, dialysis-dependent end stage renal disease, liver cirrhosis with complications, chronic ventilator dependence, major trauma, generalized autoimmune syndrome, and spinal injury/myelodysplasia). If there were more than two candidate uninfected inpatients, we chose the two that had the closest matching between HAI patients as the onset date of the S. aureus HAI case. If no suitable match was found, we reduced the matching requirement of primary specialty/subspecialty to just primary specialty. If a suitable match still could not be identified, we considered the matching process to have failed.

We used the NHI database to obtain patient data for individual matching and validation of comparability. The NHI in Taiwan has a coverage rate of 99% due to universal health insurance [24]. The NHI claims data recorded five major diagnoses (i.e. one primary diagnosis and up to four secondary diagnoses) for the patient, which were reported by the hospital based on the ICD–9–CM coding system. We ascertained the presence and type of severe illnesses using the Catastrophic Illness Registry, which is a subset of the NHI database (and thus has the same coverage rate). There are 30 major categories of catastrophic illnesses for which patient copayment can be exempted. The certification, which is strictly regulated by the NHI bureau, requires independent evaluation by two specialist physicians to confirm both the diagnosis and irreversibility of the illness [25].

Validation of Comparability

To validate comparability between the S. aureus HAI cases and matched uninfected inpatients on baseline characteristics before onset of S. aureus HAIs, we examined the between-group difference on clinical variables unrelated to HAIs (i.e. the presence of ischemic heart disease, congestive heart failure, stroke, diabetes, hypertension, elective surgical procedures, and medications for treating cardiovascular and/or neoplastic disorders).

Ascertainment of Outcomes

We derived the data on survival status and date of death using the National Death Registry (from Department of Health, Taiwan), which contains all the death certificates of Taiwanese citizens. The data on new-onset chronic ventilator dependence and dialysis-dependent end-stage renal disease were ascertained using the Catastrophic Illness Registry. To ensure a 100% one-year follow-up rate, data of both registries were updated to the end of year 2009. We used the date of Catastrophic Illness Certificate application as the onset date of chronic ventilator dependence and dialysis-dependent end-stage renal disease. To distinguish old events that were already present at admission from new-onset events that occurred after the index date, we defined the index date for S. aureus HAI patients as the onset date of the S. aureus HAI; that for uninfected patients was the admission date plus the length of stay before onset of the S. aureus HAI of the matched case. We used three linkage variables (encrypted personal ID, encrypted hospital ID, and admission date) to link the anonymized patient data between different datasets.

The data of hospital costs were obtained from the NHI dataset, which recorded the total cost (including diagnosis, laboratory, drug, ward, therapeutic-procedure, and special-material fees) for the entire hospitalization period of each patient.
**Statistical Analysis**

We compared the main outcomes between the *S. aureus* HAI group and the uninfected group using multivariate conditional logistic regression stratified by matched pairs, with adjustment for the effects of diabetes mellitus and hypertension. We compared the length of hospital stay and the hospital cost between two groups using the random effect model. All statistical analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA). Statistical significance of P values was interpreted with Bonferroni’s correction for multiple comparisons.

**Results**

The 114 hospitals reported a total of 47729 HAI cases during 2006–2008. Linking between the TNIS and the NHI dataset failed for 6587 cases (13.8%) due to inconsistency in one or more of the three linkage variables. Among the remaining 41142 HAI cases, the isolated pathogen was *S. aureus* for 4027 cases. Of them, 3563 cases met the inclusion criteria and 3070 cases were successfully matched to 6140 inpatients without HAIs (successful matching rate 86.2% [3070/3563]) (Figure 1). Compared to *S. aureus* HAI cases with successful matching, the *S. aureus* HAI cases with unsuccessful matching (n = 493) had a longer average length of stay before onset of the *S. aureus* HAI (95 vs. 20 days) and were more likely to have a severe illness at admission (14.0% vs. 3.7% for dialysis-dependent end-stage renal disease; 21.1% vs. 2.0% for chronic ventilator dependence) (all P < 0.001).

Of the 3070 *S. aureus* HAI cases, the causal *S. aureus* strains were MRSA in 2201 cases (71.7%). Patients with MRSA HAIs tended to be older (mean age: 68 vs. 62 years), had a longer average length of stay before onset of the HAI (23 vs. 13 days), and were more likely to have a severe illness at admission (4.0% vs. 2.9% for dialysis-dependent end-stage renal disease; 2.5% vs. 0.6% for chronic ventilator dependence), compared with patients with MSSA HAIs (all P < 0.001).

The baseline characteristics of the 3070 matched pairs are shown in Table 1. There was no statistically significant between-group difference in the matching variables and the comparability-validation variables, with the only exceptions of diabetes mellitus and hypertension. Compared with the *S. aureus* HAI group, the uninfected group had a slightly higher proportion of patients with diabetes mellitus (22.1% vs. 19.4%, P < 0.001) and hypertension (23.2% vs. 16.8%, P < 0.001), as well as a lower average number of diagnoses recorded in the NHI dataset (4.3 vs. 4.7, P < 0.001).

Table 2 summarizes the main outcomes. *S. aureus* HAI cases had an excess in-hospital mortality, mortality within 30 days after discharge, and one-year mortality of 19.9%, 21.1%, and 20.2%, respectively (all P < 0.001) (Table 2). The excess one-year mortality was highest for nosocomial pneumonia (28.5%) and bloodstream infection (22.3%) (Table 3). MRSA and MSSA
cases had an excess one-year mortality of 21.8% and 16.1%, respectively (Table 3 and Figure 2). *S. aureus* HAIs cases also had an excess risk for new-onset chronic ventilator dependence during hospitalization, within 30 days after discharge, and within one-year (6.8%, 7.6%, and 7.3%, respectively, all \( P < 0.001 \)). The excess risk for new-onset dialysis-dependent end-stage renal disease during hospitalization, within 30 days after discharge, and within one-year was 1.7%, 2.3%, and 2.6%, respectively (all \( P < 0.001 \)). After adjusting for the presence of diabetes mellitus and hypertension, the differences in outcomes

| Matching Variables                      | S. aureus HAI Patients (n = 3070) | Matched Patients without HAIs (n = 6140) | \( P \) value |
|-----------------------------------------|-----------------------------------|------------------------------------------|---------------|
| Age, mean±SD/median (IQR)               | 67±19/72 (56–80)                  | 67±19/72 (56–80)                         | –             |
| Gender, female (%)                      | 1051 (34.2)                      | 2108 (34.2)                              | –             |
| Type of hospital, n (%)                 |                                   |                                          |               |
| Medical center                          | 944 (30.8)                       | 1888 (30.8)                              | –             |
| Regional hospital                       | 1610 (52.4)                      | 3220 (52.4)                              | –             |
| Local hospital                          | 516 (16.8)                       | 1032 (16.8)                              | –             |
| Primary specialty,* n (%)               |                                   |                                          |               |
| Neurosurgery                            | 259 (8.4)                        | 518 (8.4)                                | –             |
| Medicine                                | 236 (7.7)                        | 472 (7.7)                                | –             |
| Surgery                                 | 170 (5.5)                        | 345 (5.6)                                | –             |
| Neurology                               | 136 (4.4)                        | 272 (4.4)                                | –             |
| Orthopedics                             | 116 (3.8)                        | 232 (3.8)                                | –             |
| Pediatrics                              | 70 (2.3)                         | 136 (2.2)                                | –             |
| Plastic Surgery                         | 61 (2.0)                         | 122 (2.0)                                | –             |
| Family Medicine                         | 48 (1.6)                         | 96 (1.6)                                 | –             |
| Severe illness, n (%)                   |                                   |                                          |               |
| Cancer                                  | 520 (17.0)                       | 1040 (17.0)                              | –             |
| dialysis-dependent End-stage renal disease | 114 (3.7)                       | 228 (3.7)                                | –             |
| Liver cirrhosis with complications      | 60 (2.0)                         | 120 (2.0)                                | –             |
| Chronic ventilator dependence           | 60 (2.0)                         | 120 (2.0)                                | –             |
| Generalized autoimmune syndrome         | 32 (0.5)                         | 16 (0.5)                                 | –             |
| Spinal injury/myelopathy                | 6 (0.2)                          | 12 (0.2)                                 | –             |
| Major trauma                            | 14 (0.5)                         | 28 (0.5)                                 | –             |

| Validation Variables                    |                                   |                                          |               |
| Diagnosis, n (%)                        |                                   |                                          |               |
| Ischemic heart disease                  | 217 (7.1)                        | 480 (7.8)                                | 0.15          |
| Congestive heart failure                | 226 (7.4)                        | 444 (7.2)                                | 0.81          |
| Stroke                                  | 424 (13.8)                       | 848 (13.8)                               | 1.0           |
| Diabetes mellitus                       | 594 (19.4)                       | 1354 (22.1)                              | 0.001\(^{\dagger}\) |
| Hypertension                            | 516 (16.8)                       | 1427 (23.2)                              | <0.001\(^{\dagger}\) |
| Procedure, n (%)                        |                                   |                                          |               |
| Total joint replacement                 | 16 (0.5)                         | 43 (0.7)                                 | 0.31          |
| Coronary artery bypass graft            | 33 (1.1)                         | 43 (0.7)                                 | 0.06          |
| Rectoscopy                              | 11 (0.4)                         | 13 (0.2)                                 | 0.19          |
| Laparoscopy                             | 6 (0.2)                          | 14 (0.2)                                 | 0.52          |
| Medication, n (%)                       |                                   |                                          |               |
| Statins                                 | 154 (5.0)                        | 310 (5.0)                                | 0.95          |
| Streptokinase                           | 17 (0.6)                         | 25 (0.4)                                 | 0.33          |
| Antigout preparations                   | 293 (9.5)                        | 506 (8.2)                                | 0.04          |
| Antineoplastic agents                   | 159 (5.2)                        | 387 (6.3)                                | 0.03          |

Abbreviations: HAI, healthcare-associated infection; SD, standard deviation; IQR, interquartile range.

\(^{*}\)Eight out of 15 primary specialties with the most patients were listed.

\(^{\dagger}\)Statistically significant, after Bonferroni correction (\( P < 0.05/13 = 0.0038 \)).

\( \text{doi:10.1371/journal.pone.0071055.t001} \)
between the *S. aureus* HAI group and the uninfected group remained highly statistically significant (all *P* < 0.001) (Table 2).

Patients with *S. aureus* HAIIs had an excess hospital stay of 12 days and an extra hospital cost of $5978 compared with the matched uninfected patients (Table 4). The differences were significant in subgroup analysis by the site of infection (bloodstream, pneumonia, urinary tract, and surgical site of infection), the type of antimicrobial resistance (MSSA and MRSA), and the presence (or absence) of severe illnesses at admission (all *P* < 0.001) (Table 4).

**Discussion**

This study is the largest cohort study to date that has investigated the negative effects of *S. aureus* HAIIs on the outcomes of hospitalized patients. Using national databases, we included 3070 inpatients with *S. aureus* HAIIs and 6140 matched uninfected inpatients. Our results show that *S. aureus* HAIIs significantly increased the risks for long-term mortality and disabilities including new-onset chronic ventilator dependence and new-onset dialysis-dependent end-stage renal disease, with an excess one-year risk of 20.2%, 7.3%, and 2.6%, respectively (all *P* < 0.001). *S. aureus* HAIIs were also associated with an excess hospital stay of 12 days and an extra hospital cost of $5978 (*P* < 0.001).

**Table 2.** Excess risks for mortality and new-onset organ failure in patients with *S. aureus* HAIIs.

| Outcomes                        | Endpoint of Observation* | *S. aureus* HAI Patients | Matched Patients without HAI | Excess Risk (%) | OR       | Adjusted OR² |
|---------------------------------|--------------------------|--------------------------|------------------------------|-----------------|----------|--------------|
| Mortality                       | Number at risk#          | 3070                     | 6140                         | –               | –        | –            |
| Discharge                       |                          | 956 (31.1)               | 691 (11.3)                   | 19.9            | 4.5⁴     | 4.3⁴         |
| 30-day after discharge          |                          | 1188 (38.7)              | 1082 (17.6)                  | 21.1            | 3.8⁴     | 3.7⁴         |
| one-year                        |                          | 1828 (59.5)              | 2416 (39.3)                  | 20.2            | 3.2⁴     | 3.1⁴         |
| Chronic ventilator dependence   | Number at risk#          | 3010                     | 6020                         | –               | –        | –            |
| Discharge                       |                          | 279 (9.3)                | 151 (2.5)                    | 6.8             | 4.8⁴     | 4.6⁴         |
| 30-day after discharge          |                          | 329 (10.9)               | 203 (3.4)                    | 7.6             | 4.2⁴     | 4.1⁴         |
| one-year                        |                          | 393 (13.1)               | 349 (5.8)                    | 7.3             | 2.8⁴     | 2.7⁴         |
| Dialysis-dependent end-stage renal disease | Number at risk# | 2956                     | 5912                         | –               | –        | –            |
| Discharge                       |                          | 77 (2.6)                 | 53 (0.9)                     | 1.7             | 3.5⁴     | 4.1⁴         |
| 30-day after discharge          |                          | 120 (4.1)                | 105 (1.8)                    | 2.3             | 2.9⁴     | 3.6⁴         |
| one-year                        |                          | 153 (5.2)                | 153 (2.6)                    | 2.6             | 2.6⁴     | 3.2⁴         |

Abbreviations: HAI, healthcare-associated infection; OR, odds ratio.

*Follow-up duration from index date to endpoint of observation.

¹Number at risk: the number of patients who have not yet developed the outcomes at admission.

²Adjusted for diabetes mellitus and hypertension.

³Statistically significant, after Bonferroni correction (all *P* < 0.05/18 = 0.0028).

doi:10.1371/journal.pone.0071055.t002
and extra hospital costs associated with *S. aureus* infections. Furthermore, our study extends the results to patients with HAIs, reported an excess 90-day crude mortality which involved smaller numbers of patients and mainly focused on surgical site infections. Using population-based data, our study validates the observed values. Thus the actual excess risks would have been higher than the underestimation for the negative impact of surgical site infections (operations) in the uninfected group would have caused an explanation for the difference is that diabetes mellitus and hypertension in the uninfected group. The most likely factors including age, gender, hospital, primary specialty/subspecialty, and underlying disease severity. Analysis of the validation variables did show a lack of difference in most baseline characteristics (e.g. the frequency of cardiovascular diseases, elective surgery, and antineoplastic agent use), with the exception of a slightly higher proportion of patients with diabetes mellitus and hypertension in the infected group. The most likely variable in the NHI database for the major diagnoses of the patient in the NHI database for the uninfected group that had a lower average number of diagnoses. Even if the result reflects a genuine difference in these two comorbidities, the higher proportions of patients with diabetes mellitus and hypertension (which may adversely affect the outcomes) in the uninfected group would have caused an underestimate for the negative impact of *S. aureus* HAIs and thus the actual excess risks would have been higher than the observed values.

Our findings on the excess mortality, prolonged hospital stay, and extra hospital costs associated with *S. aureus* HAIs are consistent with the existing literature [15–20]. Previous studies, which involved smaller numbers of patients and mainly focused on surgical site infections, reported an excess 90-day crude mortality of 10.5–16.8% for patients with *S. aureus* surgical site infections [15,17,18]. Using population-based data, our study validates the previous results and found an excess one-year mortality of 12.4%. Furthermore, our study extends the results to patients with *S. aureus* HAIs in general. We also first show that patients with *S. aureus* pneumonia and bloodstream infection suffered the highest excess one-year mortality of 28.5% and 21.3%, respectively.

In addition to an excess infection-related mortality, our study shows that *S. aureus* HAIs increase the risk for long-term disability. Severe *S. aureus* infections can cause acute organ dysfunction [26], particularly in patients with pre-existing chronic lung or renal disease(s). Blot et al. compared 85 cases of *S. aureus* bacteremia with 170 matched uninfected patients and found that the former had a significantly longer length of ventilator dependence than the latter [3]. Reach et al. composed a large study of 1575 matched pairs and found that MRSA patients were more likely to undergo mechanical ventilation than uninfected patients (excess risk: 7.5%) [27]. Our study first provides evidence on the potential irreversibility of *S. aureus* HAIs-related ventilator dependence and renal failure, showing that *S. aureus* HAIs increased the risks for new-onset chronic ventilator dependence and dialysis-dependent end-stage renal disease by 7.3% and 2.6%, respectively, compared with patients with the same type and severity of underlying disease but without HAIs. Therefore, *S. aureus* HAIs can cause irreversible organ dysfunction and profoundly affect the patient’s long-term well-being.

The excess risks for long-term mortality and disability highlight the importance to reduce occurrence of *S. aureus* HAI, which is a preventable disease. One of the main causes for the spread of MRSA within hospitals is poor hand hygiene compliance among healthcare workers [28]. Studies have found that the incidence of HAIs can be decreased by the introduction of hand hygiene programs and other measures [29]. There is growing literature supporting the beneficial effects of hand hygiene [30,31]. A systemic review of 30 intervention studies suggested that 10–70% of HAIs are probably preventable with appropriate infection control [32]. A recent randomized controlled trial proves that active surveillance and decolonization of nasal *S. aureus* carriers on admission can further reduce the incidence rate of surgical site infection [33].

### Table 3. Subgroup analysis of excess one-year mortality.

| Variables                                      | *S. aureus* HAI Patients | Matched Patients without HAIs | % Difference | P value  |
|------------------------------------------------|--------------------------|-------------------------------|-------------|---------|
| one-year mortality, n (%)                      | 3070 1828 (59.5)         | 6140 2416 (39.3)              | 20.2        | <0.001† |
| By site of infection of index *S. aureus* HAI cases |                          |                               |             |         |
| Bloodstream infection                          | 1329 878 (66.1)          | 2658 1162 (43.7)              | 22.3        | <0.001† |
| Pneumonia                                      | 785 540 (68.8)           | 1570 632 (40.3)               | 28.5        | <0.001† |
| Urinary tract infection                        | 206 111 (53.9)           | 412 186 (45.1)                | 8.7         | <0.001† |
| Surgical site infection                        | 310 102 (32.9)           | 620 127 (20.5)                | 12.4        | <0.001† |
| Others                                         | 440 197 (44.8)           | 880 309 (35.1)                | 9.7         | <0.001† |
| By antimicrobial resistance of index *S. aureus* HAI cases |                      |                               |             |         |
| MSSA                                           | 869 419 (48.2)           | 1738 558 (32.1)               | 16.1        | <0.001† |
| MRSA                                           | 2201 1409 (64.0)         | 4402 1858 (42.2)              | 21.8        | <0.001† |
| By presence of severe illnesses* at admission of index *S. aureus* HAI cases | | | | |
| No                                             | 2295 1255 (54.7)         | 4590 1491 (32.5)              | 22.2        | <0.001† |
| Yes                                            | 775 573 (73.9)           | 1550 925 (59.7)               | 14.2        | <0.001† |

Abbreviations: HAI, healthcare-associated infection; SD, standard deviation; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*.

*Any of the 7 classes of severe illnesses (cancer, dialysis-dependent end stage renal disease, liver cirrhosis with complications, chronic ventilator dependence, generalized autoimmune syndrome, spinal injury/myeleterosis, and major trauma).

†Statistically significant, after Bonferroni correction (P<0.05/10 = 0.005).

doi:10.1371/journal.pone.0071055.t003
Our results on the excess mortality/disability and excess hospital stay/costs indicate that a reduction in incidence of S. aureus HAIs can translate to improved long-term outcomes and significant cost savings, particularly when the huge financial burdens of providing long-term ventilator and dialysis services are taken into consideration.

Our study was limited by the voluntary nature of TNIS participation and HAI case notification. The 114 hospitals in current study may not represent all hospitals in Taiwan. Nevertheless, we minimize the potential effect of self-selection bias on the estimated excess risk associated with S. aureus HAIs, by individually matching the S. aureus HAI cases to uninfected inpatients by the hospital. Because the notification of HAI cases was also voluntary, it is possible that some of the 6140 matched uninfected inpatients might indeed have HAIs, which would have caused an underestimation of S. aureus HAI-associated excess risks for long-term mortality and disability. Therefore, our findings represent a conservative estimate for the negative impact of S. aureus HAIs.

Conclusion

S. aureus HAIs have substantial negative effect on the long-term outcome of hospitalized patients in terms of both mortality and disability, which should be taken into consideration in future cost-effectiveness studies of the control and prevention interventions for S. aureus HAIs.

Acknowledgments

We thank the hospitals participating in the Taiwan Nosocomial Infections Surveillance (TNIS). The National Health Insurance database and National Death Registry were kindly provided by the Collaboration Center of Health Information Application (CCHIA), Department of Health, Taiwan.
Author Contributions
Conceived and designed the experiments: CTF CHS JJY LJC. Analyzed the data: CHS. Contributed reagents/materials/analysis tools: CTF CHS

References
1. Hsueh PR, Teng LJ, Chen WH, Pan HJ, Chen ML, et al. (2004) Increasing
2. Chen ML, Chang SC, Pan HJ, Hsueh PR, Yang LS, et al. (1999) Longitudinal
3. Burton DC, Edwards JR, Jernigan JA, Fralick SK, et al. (2009) Methicillin-resistant
4. Blot SI, Vandewoude KH, Hoste EA, Colardyn FA (2002) Outcome and
5. Lodise TP, McKinnon PS (2007) Burden of methicillin-resistant
6. Cluff LE, Reynolds RC, Page DL, Breckenridge JL (1968) Methicillin-resistant
7. Julander I (1985) Unfavourable prognostic factors in endemic methicillin-resistant
8. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, et al. (2006) Early
9. Klevens RM, Edwards JR, Gaynes RP, National Nosocomial Infections
10. Fang CT, Shau WY, Hsueh PR, Chen YC, Wang JT, et al. (2006) Early
11. Boyce JM, Cookson B, Christiansen K, Hori S, Vuopio-Varkila J, et al. (2005) Comparison of mortality associated with methicillin-resistant and methicillin-susceptible Staphylococcus aureus: a meta-analysis. Ann Intern Med 142: 511–519.

12. Eber MR, Laxminarayan R, Perencevich EN, Malani A (2010) Clinical and economic outcomes attributable to health-care associated sepsis and pneumonia. Arch Intern Med 170: 347–353.
13. Lodise TP, McKinnon PS (2007) Burden of methicillin-resistant Staphylococcus aureus: focus on clinical and economic outcomes. Pharmacotherapy 27: 1001–1012.
14. Chaff LE, Reynolds RC, Page DL, Breckenridge JL (1968) Staphylococcal bacteremia and altered host resistance. Ann Intern Med 69: 859–873.
15. Julander I (1985) Unfavourable prognostic factors in methicillin-resistant Staphylococcus aureus septicaemia and endocarditis. Scand J Infect Dis 17: 179–187.
16. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, et al. (2003) Comparison of mortality associated with methicillin-resistant and methicillin-susceptible Staphylococcus aureus bacteremia: a meta-analysis. Clin Infect Dis 36: 53–59.
17. Klevens RM, Edwards JR, Gaynes RP, National Nosocomial Infections Surveillance System (2003) The impact of antimicrobial-resistant, healthcare-associated infections on mortality in the United States. Clin Infect Dis 47: 927–930.
18. Fang CT, Shau WY, Hsueh PR, Chen YC, Wang JT, et al. (2006) Early empiric glycopeptide therapy for patients with methicillin-resistant Staphylococcus aureus bacteremia: impact on the outcome. J Antimicrob Chemother 57: 511–519.
19. Boyce JM, Cookson B, Christiansen K, Hori S, Vuopio-Varkila J, et al. (2005) Methicillin-resistant Staphylococcus aureus. Lancet Infect Dis 5: 653–663.
20. Chen ML, Chang SC, Pan HJ, Hsueh PR, Yang LS, et al. (1999) Longitudinal analysis of methicillin-resistant Staphylococcus aureus isolates at a teaching hospital in Taiwan. J Formos Med Assoc 98: 426–432.
21. Hsueh PR, Teng LJ, Chen WH, Pan HJ, Chen ML, et al. (2004) Increasing prevalence of methicillin-resistant Staphylococcus aureus causing nosocomial infections at a university hospital in Taiwan from 1986 to 2001. Antimicrob Agents Chemother 40: 1361–1364.
22. Chen ML, Chang SC, Pan HJ, Hsueh PR, Yang LS, et al. (1999) Longitudinal analysis of methicillin-resistant Staphylococcus aureus isolates at a teaching hospital in Taiwan. J Formos Med Assoc 98: 426–432.
23. Hsueh PR, Teng LJ, Chen WH, Pan HJ, Chen ML, et al. (2004) Increasing prevalence of methicillin-resistant Staphylococcus aureus causing nosocomial infections at a university hospital in Taiwan from 1986 to 2001. Antimicrob Agents Chemother 40: 1361–1364.
24. Whitty M, McLois ML, Berry G (2001) Risk of death from methicillin-resistant Staphylococcus aureus bacteremia: a meta-analysis. Med J Aust 175: 226–227.
25. Anderson DJ, Kaye KS, Chen LF, Schmader KE, Choi Y, et al. (2009) Clinical and financial outcomes due to methicillin-resistant Staphylococcus aureus surgical site infection: a multi-center matched outcomes study. PLoS One 4: e6305.
26. Nixon M, Jackson B, Varghese P, Jenkins D, Taylor G (2006) Methicillin-resistant Staphylococcus aureus on orthopaedic wards: incidence, spread, mortality, cost and control. J Bone Joint Surg Br 88: 612–617.
27. McGarry SA, Engemann JJ, Schmader K, Sexton DJ, Kaye KS (2004) Surgical-site infection due to Staphylococcus aureus among elderly patients: mortality, duration of hospitalization, and cost. Infect Control Hosp Epidemiol 25: 461–467.
28. Engemann JJ, Carmeli Y, Cosgrove SE, Fowler VG, Bronstein MZ, et al. (2003) Adverse clinical and economic outcomes attributable to methicillin resistance among patients with Staphylococcus aureus surgical site infection. Clin Infect Dis 36: 592–598.
29. Abramson MA, Sexton DJ (1999) Nosocomial methicillin-resistant and methicillin-susceptible Staphylococcus aureus primary bacteremia: at what costs? Infect Control Hosp Epidemiol 20: 408–411.
30. Chais C, Durand-Zaleski I, Alverici C, Brua-Buisson C (1999) Control of endemic methicillin-resistant Staphylococcus aureus: a cost-benefit analysis in an intensive care unit. JAMA 282: 1745–1751.
31. Leibovici L, Samra Z, Konigshofer H, Drucker M, Ashkenazi S, et al. (1995) Long-term survival following bacteremia or fungemia. JAMA 274: 807–812.
32. Centers for Disease Control (Taiwan) (2009) Statistics of communicable diseases and surveillance report 2008. Available: http://www.cdc.gov.tw/uploads/files/307c10eb-9859-47a-bb6a-ab33aa0b6e5e.pdf. Accessed 1 March 2013.
33. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM (1988) CDC definitions for nosocomial infections, 1988. Am J Infect Control 16: 128–140.
34. Bureau of national health insurance (Taiwan) (2010) National health insurance in Taiwan 2011. Available: http://www.nhi.gov.tw/Resource/webdata/30774_1_NHI%20IN%20TAIWAN%202011%20ANNUAL%20REPORT.pdf. Accessed 1 March 2013.
35. Bureau of national health insurance (Taiwan) (2011) Catastrophic Illness Patients. Available: http://www.nhi.gov.tw/English/webdata/webdata.aspx?menu=1&menu_id=596&WD_ID=596&webdata_id=3180. Accessed 1 March 2013.
36. Martin GS, Mannino DM, Eaton S, Moss M (2005) The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 348: 1546–1554.
37. Resch A, Wilke M, Fink C (2009) The cost of resistance: incremental cost of methicillin-resistant Staphylococcus aureus (MRSA) in German hospitals. Eur J Health Econ 10: 287–297.
38. Burke JP (2003) Infection control – a problem for patient safety. N Engl J Med 348: 651–656.
39. Sroka S, Gastmeier P, Meyer E (2010) Impact of alcohol hand-rub use on meticillin-resistant Staphylococcus aureus: an analysis of the literature. J Infect Hosp Infect 74: 204–211.
40. Tseng SH, Lee CM, Lin TY, Chang SC, Chang FY (2011) Emergence and spread of multi-drug resistant organisms: think globally and act locally. J Microbiol Immunol Infect 44: 157–163.
41. Chen YC, Sheng WH, Wang JT, Chang SC, Lin HC, et al. (2011) Effectiveness and limitations of hand hygiene promotion on decreasing healthcare-associated infections. PLoS One 6: e27163.
42. Harbach S, Sax H, Gastmeier P (2003) The preventable proportion of nosocomial infections: an overview of published reports. J Hosp Infect 54: 258–266.
43. Bode LG, Khaymsans JA, Wertheim HF, Bogaers D, Vandenhroucke-Grans CM, et al. (2010) Preventing surgical-site infections in nasal carriers of Staphylococcus aureus. N Engl J Med 362: 9–17.

JJY SHT LJC. Wrote the paper: CTF CHS. Interpreted data: CTF CHS SCC JJY

PLOS ONE | www.plosone.org 8 August 2013 | Volume 8 | Issue 8 | e71055