Length of stay, hospitalisation costs and in-hospital mortality of methicillin-susceptible and methicillin-resistant Staphylococcus aureus bacteremia in Japan

Public Health

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--Manuscript Draft--

Manuscript Number:	PUHE-D-21-01030R1
Article Type:	Original Research
Keywords:	MRSA; bacteremia; length of stay; hospitalization cost; Japan
Corresponding Author:	Shinya Tsuzuki Tokyo, JAPAN
First Author:	Shinya Tsuzuki
Order of Authors:	Shinya Tsuzuki
	Jiefu Yu
	Nobuaki Matsunaga
	Norio Ohmagari
Abstract:	Objectives To examine the length of stay, hospitalization cost, and case fatality of methicillin-susceptible and -resistant Staphylococcus aureus (MSSA and MRSA) bacteremia in Japan. Study design Retrospective cohort study. Patients with a diagnosis of Staphylococcus aureus bacteremia admitted to a tertiary care hospital (National Center for Global Health and Medicine [NCGM]) in Tokyo, Japan, between 1 st January 2016 and 31 st December 2020 . Methods We combined Japan Nosocomial Infections Surveillance data and Diagnosis Procedure Combination data at NCGM from 2016 to 2020. The data were stratified into MSSA and MRSA groups. Length of stay (LoS), LoS after submission of a blood culture specimen (LoS-after), hospitalization cost, hospitalization cost per day, and clinical outcome were compared after propensity score matching. Results Median LoS was 46 (IQR 28.5-64.5) days in the MSSA group and 66 (IQR 40-91) days in the MRSA group (p = 0.020). Median LoS-after was 38 (IQR 25-62.5) days and 45 (IQR 24-63) days (p = 0.691), respectively. Median hospitalization cost was significantly higher in the MRSA group (26,035 [IQR 18,154-47,362] USD) than in the MSSA group (19,823 [IQR 13,764-32,042] USD) (p = 0.036) but cost per day was not (MRSA: 528.9 [IQR 374.9-647.4] USD; MSSA: 455.6 [IQR 359.2-701.7] USD; p = 0.990). Case fatality rate was higher in the MRSA group than in the MSSA group (22/60 vs. 9/60, p = 0.012). Conclusions Patients with MRSA bacteremia had longer LoS and higher costs than those with MSSA bacteremia. However, LoS-after and hospitalization cost per day were not different. The longer LoS than that of other countries might contribute to the higher disease burden of S. aureus bacteremia in Japan.

Length of stay, hospitalization cost, and in-hospital mortality of methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* bacteremia in Japan

Shinya Tsuzuki, MD, MSc[1, 2*], Jiefu Yu, MSc[1], Nobuaki Matsunaga, MD, PhD[1], Norio Ohmagari, MD, PhD[1,3]

[1]AMR Clinical Reference Center, National Center for Global Health and Medicine, Tokyo, Japan

[2]Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium

[3]Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan

***Corresponding author**

AMR Clinical Reference Center, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan

Tel: +81(0)332027181

Email: stsuzuki@hosp.ncgm.go.jp

Acknowledgments

Statements of ethical approval: This study was approved by the Ethics Committee of National Center for Global Health and Medicine, Tokyo, Japan (approval number, NCGM-G-003606-00).

Funding: This study was supported by a Ministry of Health, Labour and Welfare (MHLW) research grant of Japan (20HA2003).

Competing interests: We declare no competing interests.

Data sharing: Data used in this study are available from the corresponding author upon reasonable request.

Contributors: ST and NO conceived the study. JY collected and managed the data. ST performed statistical analyses and drafted the first draft of the manuscript. NM, JY, and NO critically reviewed the manuscript and all authors approved the final version of the manuscript.

Resubmission Manuscript

Manuscript Number: PUHE-D-21-01030

Article Title: Length of stay, hospitalization cost, and in-hospital mortality of methicillin-susceptible and methicillin-resistant Staphylococcus aureus bacteremia in Japan

June 28, 2021

Andrew Lee, Joanne Morling

Editors-in-Chief

Public Health

Dear Drs. Lee and Morling,

Thank you very much for giving us the opportunity to revise our manuscript. We appreciate the reviewers' careful review and constructive suggestions. Please find our point-by-point responses to the comments below in blue italics. Changes made in the main body of the manuscript are indicated using Track Changes.

We hope that the manuscript is now suitable for publication in *Public Health*

and look forward to hearing from you.

Sincerely,

Shinya Tsuzuki, MD, MSc

AMR Clinical Reference Center,

National Center for Global Health and Medicine

stsuzuki@hosp.ncgm.go.jp

In addition to the reviewer comments below the Editor suggests that the methods section also needs to be revised to add more detail so that the analysis can be replicated by others (more detail on what analysis was carried out exactly). However, the Editor highlights that it also needs to be succinct.

We appreciate the Editor's suggestion and have substantially revised the "Methods". It is now divided into the following subsections: "Data source and curation", "Definition of cases", "Hospitalization cost", "Statistical analysis" and "Ethics approval". More detailed information was added to each subsection in response to the reviewers' comments. We have endeavoured to be as succinct as possible. In addition, we have uploaded the R code used in this study to enable readers to replicate the results. It is difficult for us to make our data publicly available due to ethical concerns, but the data will be available upon reasonable request to the corresponding author.

Reviewer #1: Abstract/ Methodology - Line 13 and Line 60 - please mention exact study dates Eg. 1st January 2016 - 31st December 2020

Thank you for your suggestion. Our study period ran from 1 January 2016 to 31 December 2020, as you expected.

Methodology:

Please provide what definition was used for MRSA and MSSA bacteremia in this study, were ICD-10 codes used? Or a clinical definition?

We appreciate your comment. We followed the definitions provided by the Japan Nosocomial Infections Survey (JANIS), which are based on those of the Clinical Laboratory Standards Institute (CLSI). The definitions have been detailed in the main manuscript text.

Mention more in detail about data linkage, how data was extracted and stored, who had access, was the data linkage key available, was data de-identified or not?

Please include a section on how costing was done to arrive at hospitalization costs

Thank you very much for your constructive suggestion. The data aggregation process has now been detailed in the "Data source and curation" subsection in the "Methods".

As for costing, please refer to the "Hospitalization cost" subsection in the "Methods", where we describe the component of cost in this study. It includes drug cost, treatment and operation cost, examination cost and accommodation cost.

Results:

I see that authors have reported costs in USD to allow for international comparison, would be good to have the same results mentioned in JPY as well for Japanese readers of the article.

We have made the appropriate change.

Discussion:

Lines 158, 160 - mentions case fatality risk - I would suggest using the term case fatality rate

We have used your suggested term.

Include which component of hospitalization cost in both groups was high - was it bed

charge, treatment cost, etc?? Would be a value add to the analysis which has been done, if this can be described

Thank you for your insightful comment. We have added a new figure (Figure 3) that shows the breakdown of the accumulated hospitalization cost between 2016 and 2020. Accommodation cost accounted for 59.1% of the total cost in the MSSA group. Similarly, the accommodation cost accounted for 52.6% of the total cost in the MRSA group.

Curious to know why Japan has such high LoS - I do acknowledge that authors have touched upon it briefly and recommended further research

We appreciate your suggestion. One of our key references (Tiessen et al., DOI: 10.1177/0951484813512287) stated that "non-clinical factors contribute to sustained international differences in length of stay. These factors may include professional or cultural norms, differing payment schemes and access to long-term care facilities". We agree with their viewpoint and have discussed this aspect in the revised manuscript.

Reviewer #2: Comments

1. The revised introduction should state the contribution of the paper to the earlier empirical literature.

Thank you for your insightful suggestion. We have added a more detailed explanation of the contribution of the present study. As described in the original manuscript, information on LoS and hospitalization cost is not widely available in Japan. This made it difficult for us to appropriately assess the burden of each disease. Our results might be used as an indicator in the evaluation of disease burden in the context of an international comparison.

2. The revised introduction should motivate the empirical context of the study.

As in our answer to the previous question, we have few data on LoS and hospitalization cost, which makes it difficult to estimate the precise burden of disease. For example, we know that our LoS is longer than in other countries by comparison with OECD evidence but we do not know to what extent. Our results elucidate to what extent the LoS of

bacteremia is longer, which will enable us to more precisely estimate the disease burden of bacteremia.

3. What is the external validity of the findings that are presented in the paper?

We thank you for giving us an opportunity to discuss this issue. As we explained in the "Discussion", one of the limitations of our results is they are based on data from a single national centre hospital. The next step would be a multicenter study. Nevertheless, our results are the first step in elucidating the difference in LoS between Japan and other countries because other studies also found a longer LoS in Japan for other diseases compared with other countries. Furthermore, the causes of this difference would also be an interesting topic for further consideration.

4. Are all relevant (economic) costs captured in the study?

Thank you for giving us a chance to explain this aspect in more detail. We have added a "Hospitalization cost" subsection to the "Methods" and described the component of cost in this study. It includes drug cost, treatment and operation cost, examination cost,

accommodation cost and other expenses. In other words, "hospitalization cost" in this study refers to the cost paid by acute healthcare facilities and does not include the cost of long-term care and expenses paid by patients (e.g., transportation fees). As described in the original manuscript, "direct costs from the healthcare payer perspective" were captured in this study.

5. The paper should state more practical policy lessons that stem from the estimation results that are presented in the paper.

Thank you for your suggestion. As now stated in the last paragraph, we can reduce the disease burden of S. aureus *bacteremia if the LoS in Japan is unnecessary longer than that in other countries. However, it will be important to examine why the LoS is so long in Japan to take appropriate countermeasures.*

Length of stay, hospitalization cost, and in-hospital mortality of methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* bacteremia in Japan

Summary

Objectives

To examine the length of stay, hospitalization cost, and case fatality of methicillin-susceptible and -resistant *Staphylococcus aureus* (MSSA and MRSA) bacteremia in Japan.

Study design

Retrospective cohort study.

Patients with a diagnosis of *Staphylococcus aureus* bacteremia admitted to a tertiary care hospital (National Center for Global Health and Medicine [NCGM]) in Tokyo, Japan, between 1st January 2016 and 31st December 2020.

Methods

We combined Japan Nosocomial Infections Surveillance data and Diagnosis Procedure Combination data at NCGM from 2016 to 2020. The data were stratified into MSSA and MRSA groups. Length of stay (LoS), LoS after submission of a blood culture specimen (LoS-after), hospitalization cost, hospitalization cost per day, and clinical

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outcome were compared after propensity score matching.

Results

Median LoS was 46 (IQR 28.5-64.5) days in the MSSA group and 66 (IQR 40-91) days in the MRSA group (p = 0.020). Median LoS-after was 38 (IQR 25-62.5) days and 45 (IQR 24-63) days (p = 0.691), respectively. Median hospitalization cost was significantly higher in the MRSA group (26,035 [IQR 18,154-47,362] USD) than in the MSSA group (19,823 [IQR 13,764-32,042] USD) (p = 0.036) but cost per day was not (MRSA: 528.9 [IQR 374.9-647.4] USD; MSSA: 455.6 [IQR 359.2-701.7] USD; p = 0.990). Case ~~fatality risk~~fatality rate was higher in the MRSA group than in the MSSA group (22/60 vs. 9/60, p = 0.012).

Conclusions

Patients with MRSA bacteremia had longer LoS and higher costs than those with MSSA bacteremia. However, LoS-after and hospitalization cost per day were not different. The longer LoS than that of other countries might contribute to the higher disease burden of *S. aureus* bacteremia in Japan.

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Keywords: MRSA, bacteremia, l~~L~~ength of stay, hospitalization cost, Japan

Introduction

Staphylococcus aureus is one of the most important causes of bacteremia and poses a substantial burden to society.[1–6] Because *S. aureus* bacteremia requires long-term parenteral antibiotic therapy, its disease burden is not limited to high mortality but also extends to economic aspects.[7,8] In addition, methicillin-resistant strains (MRSA) might have a heavier burden than susceptible strains (MSSA).[9] However, to our knowledge, there is no solid evidence on the difference in the disease burden of bacteremia between MRSA and MSSA.

Length of stay (LoS) and hospitalization cost are important indicators for estimating the burden of diseases on healthcare facilities. According to the Organisation for Economic Co-operation and Development (OECD), there is wide international variation in LoS, with Japan showing a markedly longer LoS than the worldwide average (16.1 days vs 6.6 days in 2018).[10] Although we know that the disease burden due to LoS is larger in Japan than in other countries, few studies have investigated LoS in Japan in detail. For hospitalization cost, scarce evidence is available from Japan. Only a few previous studies have reported hospitalization costs in Japan but they focused on specific diseases other than bacteremia.[11–13] Consequently, it is difficult to estimate the actual disease burden of bacteremia in Japan and to compare it with that in

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other developed countries.

The main objective of this study was to examine the outcomes of MRSA and MSSA bacteremia in terms of LoS, hospitalization cost, and case fatality in a tertiary care hospital in Japan. These results will provide novel evidence on LoS and hospitalization cost and permit comparisons in the area of infectious diseases. Such evidences will enable us to more precisely estimate the burden of each disease, and will be a good indicator for health policy decision makers.

Methods

Data source and curation

We obtained Japan Nosocomial Infections Surveillance (JANIS)[14] data which include information about microorganisms and Diagnosis Procedure Combination (DPC) data which includes information on patients' background, hospitalization cost, and LoS recorded between 1 January 2016 and 31 December 2020 from ~~the~~ National Center for Global Health and Medicine (NCGM).

The data were stored on a hard disk in a locked cabinet and only the authors of this study had access to them. The data were de-identified and we extracted only cases with a diagnosis of blood stream infections and a detection record of *S. aureus* from a

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blood culture specimen during the same admission period. We next merged the JANIS data and DPC data by sex, age, date of birth, date of admission, and date of discharge and then stratified the merged data into MSSA and MRSA groups.

~~After extracting the data of patients diagnosed as having bacteremia and whose blood culture results were positive for *S. aureus*, we stratified cases into a methicillin-susceptible (MSSA) group and a methicillin-resistant (MRSA) group.~~

Definition of cases

Each *S. aureus* detected from blood specimen was counted as one case of blood stream infections. To avoid duplication from the same patient, we included only one specimen from the same admission data (i.e. if one patient was admitted twice for *S. aureus* bacteremia in different years, they were counted as two cases).

The criteria for judging the antimicrobial susceptibility of each bacterium were in accordance with the regulations of JANIS, which follows the criteria defined by the Clinical Laboratory Standards Institute (CLSI)[15]. MRSA was defined as *S. aureus* resistant to oxacillin and/or cefoxitin.

Hospitalization cost

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We defined hospitalization cost in this study as direct costs from the healthcare payer perspective and then obtained the hospitalization cost of each blood stream infection case through aggregation: 1) prescription cost of drugs; 2) treatment and operation cost; 3) examination cost including image inspections; 4) accommodation cost; and 5) other expenses.

Statistical analysis

LoS, LoS after submission of a blood culture specimen (LoS-after), total hospitalization cost, hospitalization cost per day ~~(direct costs from healthcare payer perspective)~~, and clinical outcome were compared between the groups after propensity score matching (one-to-one nearest matching, caliper = 0.20) to adjust for the influence of age and sex.[16,17] An absolute standardized mean difference of each covariate (age and sex) above 10% in matched data was regarded as a clinically significant difference, and all such differences were within 10%. In addition, we aggregated the data of all patients admitted to NCGM in the observation period to calculate the LoS and hospitalization cost for all causes of admission.

Two-sided *p* values less than 0.05 were considered statistically significant. All statistical analyses were performed using R version 4.0.3.[18]

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Ethics approval

This study was approved by the Ethics Committee of National Center for Global Health and Medicine, Tokyo, Japan (approval number, NCGM-G-003606-00).

Results

Table 1 shows the LoS and hospitalization cost of all patients admitted to NCGM between 2016 and 2020 (i.e., not limited to those with *S. aureus* bacteremia). In total, median hospitalization cost per patient was 5,162 (interquartile range [IQR] 2,745-10,142) USD and median LoS was 7 (IQR 3-15) days. Among all age groups, neonatal patients had the highest hospitalization cost (median 14,432 USD; IQR 8,162-28,311 USD) and the longest LoS (median 13 days; IQR 8-29 days).

(Table 1)

In the population of interest, median LoS was 46 (IQR 28.5–64.5) days in the MSSA group and 66 (IQR 40-91) days in the MRSA group. Median LoS-after was 38 (IQR 25–62.5) days in the MSSA group and 45 (IQR 24-63) days in the MRSA group.

Median hospitalization cost and cost per day were respectively 19,823 (IQR 13,764–32,042) USD and 455.6 (IQR 359.2–701.7) USD in the MSSA group and 26,035 (IQR 18,154-47,362) USD and 528.9 (IQR 374.9-647.4) USD in the MRSA group.

The Wilcoxon rank sum test revealed that LoS and hospitalization cost significantly differed between the groups (p = 0.020 and 0.036, respectively), unlike LoS-after and hospitalization cost per day (p = 0.691 and 0.990, respectively). The case fatality rate was higher in the MRSA group (22/60) than in the MSSA group (9/60) according to Fisher's exact test (p = 0.012). Table 2 shows the results before propensity score matching, and Table 3 shows the results after matching. Figures 1 and 2 are violin plots of LoS and hospitalization cost by strain, respectively.

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(Table 2)

(Table 3)

(Figure 1)

(Figure 2)

Figure 3 describes the breakdown of hospitalization cost for each group.

(Figure 3)

Accommodation cost accounted for more than half of the total hospitalization cost in both groups (59.1% in the MSSA group and 52.6% in the MRSA group). The proportion of the treatment cost was higher in the MRSA group than in the MSSA group (20.6% and 13.7%, respectively).

Discussion

To our knowledge, this is the first study examining the difference in LoS and hospitalization cost between MSSA and MRSA in Japan. In our results, median LoS of all-cause admission was substantially shorter than reported by the OECD.[10] This difference might be due to the calculation methods used. While the OECD reported the average number of days spent by patients in hospital, which is generally measured by dividing the total number of days stayed by all inpatients during a year by the number of admissions or discharges, we used the median LoS of each patient. Therefore, the 16.1

days reported by the OECD would be greatly influenced by outliers (i.e., the extremely long LoS of some patients). Nevertheless, 7 days is longer than the average LoS worldwide (6.6 days) and that in~~of~~ the US (5.5 days).[10]

Notably, the LoS of patients with *S. aureus* bacteremia in Japan is substantially longer than that in other countries. Cosgrove and colleagues reported that the median LoS for MSSA and MRSA bacteremia in the US was 7 and 9 days, respectively.[19] According to Thampi and colleagues, the median LoS of such patients in Canada was 14 and 22.5 days, respectively.[20] Another study from the Greater Toronto area found a median LoS for *S. aureus* bacteremia of 17 days.[21] In contrast, our results indicated that patients with *S. aureus* bacteremia in Japan are hospitalized for a median 49 days, which is about three times as long as that reported previously in other countries. Even when the data are limited to LoS-after (i.e., LoS after submission of a blood culture), this amounts to twice as long as that reported previously in other countries. Given these results, it is not difficult to imagine that the disease burden of *S. aureus* bacteremia will be greater in Japan than in other countries.

The cause of the considerable international differences in LoS is not clear, but, Tiessen and colleagues have obtained some interesting results.[22] Although their study examined the LoS of acute myocardial infarction, they observed a trend similar to that

of our results. In their opinion, their results can be explained by nonclinical factors such as professional/cultural norms and differences in healthcare schemes. For instance, acute care hospitals in Japan are generally equipped with a larger supply of acute care beds but, a small supply of long-term care beds. This combination should theoretically result in longer acute care stays. In addition, hospital ownership in Japan would also influence the results. Private for-profit organizations perhaps act to fill their capacity, which is higher than that of their counterpart, to maximize revenues. These hypotheses should be carefully examined in future work.

Meanwhile, we should also note that, although there was a difference in total LoS between MSSA and MRSA in our study, there was no substantial difference in LoS-after. This is a markedly different result from that of previous studies.[9,23] Generally speaking, the presence of antibiotic resistance appears to increase LoS and hospitalization costs. This phenomenon is probably related to Japanese healthcare systems and customs. Because residence in a long-term care facility is one of the risk factors of MRSA infection,[24] the longer LoS might be attributable to an increase in novel MRSA bacteremia because patients who tend to stay in the hospital longer also tend to be infected with MRSA. It is possible that the long LoS in Japan is not only unnecessary, but also increases the number of infected cases. Because the LoS-after in

Japan is substantially longer than the appropriate duration of antibiotic therapy for *S. aureus* bacteremia,[25] the difference in the recommended duration of antibiotic therapy between MSSA and MRSA does not explain the difference in LoS-after between these strains.

The hospitalization cost of *S. aureus* bacteremia in Japan is neither expensive nor cheap compared with other developed countries. Thampi and colleagues reported that *S. aureus* bacteremia costs about 12,000 USD per case in Canada.[20] In contrast, it costs more than 37,000 USD in the US.[23] As described above, the LoS in Japan is clearly longer than that in these countries, but the hospitalization cost per day in Japan may be less expensive. In addition, the hospitalization cost per day in Japan is not substantially different between MSSA and MRSA. This result is compatible with that of a recent study from the US,[26] although it contradicts the results of older studies.[19,27–31]

In terms of the clinical outcome of *S. aureus* bacteremia, the case ~~fatality risk~~fatality rate of 24.5% in this study is also similar to that in previous studies.[21,32] However, the difference in the case ~~fatality risk~~fatality rate between MSSA and MRSA is clear in our study, in contrast to a recent study.[26] This can be attributed to the nature of our data, which are a combination of microbiological test results and patients' claim data and~~,~~ which made it difficult to adjust for confounding factors associated with

prognosis.

The present study has several limitations. First, our results are based on data from a single facility. Although our facility is the largest medical center hospital in Japan in terms of infectious diseases, the number of bacteremia cases was limited and biases due to the characteristics of the facility cannot be removed. Therefore, representativeness will be a major concern for our results. Next, as explained in the previous paragraph, our data do not include the full characteristics of each patient. Although we adjusted for age and sex by propensity score matching, other confounding factors probably affected the results. Third, our claims data capture the cost incurred by the facility. Because the Japanese health insurance system adopts the Diagnosis Procedure Combination/Per-Diem Payment System, the claims data do not precisely reflect the actual cost paid by the government to the facility. In other words, our estimated hospitalization cost might be overestimated if we regard the "healthcare payer" as being the Japanese government.

Despite these limitations, our results provide necessary evidence for international comparisons of the disease burden of *S. aureus* bacteremia. At our hospital in Japan, patients with MRSA bacteremia had longer hospital stays and higher costs than those with MSSA bacteremia. However, the LoS-after and hospitalization cost per day did not differ. Furthermore, the markedly longer LoS in Japan compared with other countries

would be of major interest. Further studies of this long LoS in Japan and its reasons based on multicenter, national-level data are necessary because a longer LoS would be a major cause of heavier disease burden for the same disease in Japan compared with other countries. These novel findings might contribute to reduce the burden and medical expenses of *S. aureus* bacteremia in Japan because the LoS in Japan may be unnecessarily longer than that in other countries and causes additional productivity loss and medical costs.

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Acknowledgments

Statements of ethical approval: This study was approved by the Ethics Committee of National Center for Global Health and Medicine, Tokyo, Japan (approval number, NCGM-G-003606-00).

Funding: This study was supported by a Ministry of Health, Labour and Welfare (MHLW) research grant of Japan (20HA2003).

Competing interests: We declare no competing interests.

Data sharing: Data used in this study are available from the corresponding author upon reasonable request.

Contributors: ST and NO conceived the study. JY collected and managed the data. ST performed statistical analyses and drafted the first draft of the manuscript. NM, JY, and NO critically reviewed the manuscript and all authors approved the final version of the manuscript.

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Table 1. Cost and length of stay of all patients in the National Center for Global Health and Medicine, 2016-2020

Age group	Cost (USD*)	Cost (JPY)	Length of stay (days)
Neonates	14432 (8162-28311)	1587565 (897835-3114155)	13 (8-29)
Infants	4553 (3446-6390)	500870 (379080-702890)	6 (4-8)
1-14 years	5145 (3605-6921)	566000 (396555-761280)	5 (3-7)
15-64 years	4808 (2529-9143)	528882 (278230-1005783)	7 (3-13)
65-89 years	5219 (2696-11235)	574105 (296603-1235814)	8 (2-17)
90 years and older	6969 (3706-13010)	766628 (407668-1431061)	12 (5-25)
Total	5162 (2745-10142)	567800 (301936-1115629)	7 (3-15)

Values are shown as the median (interquartile range).

*1 USD = 110 JPY.

Table 2. Length of stay, hospitalization cost, and in-hospital mortality of patients with *S. aureus* bacteremia in the National Center for Global Health and Medicine, 2016-2020

	MSSA (n=84)	MRSA (n=63)	Total (n=147)
Age	72 (50-82)	76 (64-89)	74 (58-85)
Male sex	44 (52.4)	35 (55.6)	79 (53.7)
LoS (days)	40 (27.5-64.5)	66 (37.5-87)	49 (29-76)
LoS-after (days)*	32 (22-59.5)	43 (23-62)	32 (17-56)
Hospitalization cost (USD)**	20884 (13880-33951)	27798 (18252-47543)	22902 (15699-43330)
Hospitalization cost (JPY)	2297240 (1526856-3734595)	3057807 (2007727-5229778)	2519214 (1726905-4766352)
Hospitalization cost per day (USD)**	401 (150-1111)	496 (231-1215)	488 (374-719)
Hospitalization cost per day (JPY)	44085 (16527-122191)	54518 (25374-133648)	53651 (41181-79102)
In-hospital death	12 (14.3)	24 (38.1)	36 (24.5)

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MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA~~RF~~, methicillin-resistant *Staphylococcus aureus*; LoS, length of stay.

Values are shown as the median (interquartile range) or number (percentage).

*Length of stay after blood culture submission.

**1 USD = 110 JPY.

Table 3. Comparison of length of stay, hospitalization cost, and in-hospital mortality of MSSA and MRSA bacteremia after propensity score matching

	MSSA (n=60)	MRSA (n=60)	*p*-value†
Age	**76 (66-83)**	**76.5 (65.5-89)**	**0.303**
Male	**33 (55.0)**	**32 (53.3)**	**1.0**
LoS (days)	**46 (28.5-64.5)**	**66 (40-91)**	**0.020**
LoS-after (days)*	**38 (25-62.5)**	**45 (24-63)**	**0.691**
Hospitalization cost (USD)**	**19823 (13764-32042)**	**26035 (18154-47362)**	**0.036**
Hospitalization cost (JPY)	**2180493 (1514005-3524635)**	**2863872 (1996922-5209858)**	**0.036**
Hospitalization cost per day (USD)**	**456 (359-702)**	**529 (375-647)**	**0.990**
Hospitalization cost per day (JPY)	**50113 (39516-77191)**	**58174 (41238-71212)**	**0.990**
In-hospital death	**9 (15.0)**	**22 (36.7)**	**0.012**

MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA~~RF~~, methicillin-resistant

Staphylococcus aureus; LoS, length of stay.

Values are shown as median (interquartile range) or an absolute number (percentage).

*Length of stay after blood culture submission.

**1 USD = 110 JPY.

†Mann-Whitney test for continuous variables and Fischer's exact test for binary variables.

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Figure legends

Figure 1. Length of stay after blood culture submission by strain

MSSA, methicillin-susceptible *Staphylococcus aureus*; RF, methicillin-resistant *Staphylococcus aureus*.

Figure 2. Hospitalization cost per day by strain

MSSA, methicillin-susceptible *Staphylococcus aureus*; RF, methicillin-resistant *Staphylococcus aureus*.

Figure 3. Breakdown of the total hospitalization cost from 2016 to 2020

The horizontal axis represents the accumulated hospitalization cost during the study period.

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Length of stay, hospitalization cost, and in-hospital mortality of methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* bacteremia in Japan

Summary

Objectives

To examine the length of stay, hospitalization cost, and case fatality of methicillin-susceptible and -resistant *Staphylococcus aureus* (MSSA and MRSA) bacteremia in Japan.

Study design

Retrospective cohort study. Patients with a diagnosis of *Staphylococcus aureus* bacteremia admitted to a tertiary care hospital (National Center for Global Health and Medicine [NCGM]) in Tokyo, Japan, between 1st January 2016 and 31st December 2020.

Methods

We combined Japan Nosocomial Infections Surveillance data and Diagnosis Procedure Combination data at NCGM from 2016 to 2020. The data were stratified into MSSA and MRSA groups. Length of stay (LoS), LoS after submission of a blood culture specimen (LoS-after), hospitalization cost, hospitalization cost per day, and clinical

outcome were compared after propensity score matching.

Results

Median LoS was 46 (IQR 28.5-64.5) days in the MSSA group and 66 (IQR 40-91) days in the MRSA group (p = 0.020). Median LoS-after was 38 (IQR 25-62.5) days and 45 (IQR 24-63) days (p = 0.691), respectively. Median hospitalization cost was significantly higher in the MRSA group (26,035 [IQR 18,154-47,362] USD) than in the MSSA group (19,823 [IQR 13,764-32,042] USD) (p = 0.036) but cost per day was not (MRSA: 528.9 [IQR 374.9-647.4] USD; MSSA: 455.6 [IQR 359.2-701.7] USD; p = 0.990). Case fatality rate was higher in the MRSA group than in the MSSA group (22/60 vs. 9/60, p = 0.012).

Conclusions

Patients with MRSA bacteremia had longer LoS and higher costs than those with MSSA bacteremia. However, LoS-after and hospitalization cost per day were not different. The longer LoS than that of other countries might contribute to the higher disease burden of *S. aureus* bacteremia in Japan.

Keywords: MRSA, bacteremia, length of stay, hospitalization cost, Japan

Introduction

Staphylococcus aureus is one of the most important causes of bacteremia and poses a substantial burden to society.[1–6] Because *S. aureus* bacteremia requires long-term parenteral antibiotic therapy, its disease burden is not limited to high mortality but also extends to economic aspects.[7,8] In addition, methicillin-resistant strains (MRSA) might have a heavier burden than susceptible strains (MSSA).[9] However, to our knowledge, there is no solid evidence on the difference in the disease burden of bacteremia between MRSA and MSSA.

Length of stay (LoS) and hospitalization cost are important indicators for estimating the burden of diseases on healthcare facilities. According to the Organisation for Economic Co-operation and Development (OECD), there is wide international variation in LoS, with Japan showing a markedly longer LoS than the worldwide average (16.1 days vs. 6.6 days in 2018).[10] Although we know that the disease burden due to LoS is larger in Japan than in other countries, few studies have investigated LoS in Japan in detail. For hospitalization cost, scarce evidence is available from Japan. Only a few previous studies have reported hospitalization costs in Japan but they focused on specific diseases other than bacteremia.[11–13] Consequently, it is difficult to estimate the actual disease burden of bacteremia in Japan and to compare it with that in

other developed countries.

The main objective of this study was to examine the outcomes of MRSA and MSSA bacteremia in terms of LoS, hospitalization cost, and case fatality in a tertiary care hospital in Japan. These results will provide novel evidence on LoS and hospitalization cost and permit comparisons in the area of infectious diseases. Such evidence will enable us to more precisely estimate the burden of each disease and will be a good indicator for health policy decision makers.

Methods

Data source and curation

We obtained Japan Nosocomial Infections Surveillance (JANIS)[14] data, which include information on microorganisms, and Diagnosis Procedure Combination (DPC) data, which include information on patients' background, hospitalization cost, and LoS recorded between 1 January 2016 and 31 December 2020 from National Center for Global Health and Medicine (NCGM).

The data were stored on a hard disk in a locked cabinet and only the authors of this study had access to them. The data were de-identified and we extracted only cases with a diagnosis of blood stream infection and a detection record of *S. aureus* from a

blood culture specimen during the same admission period. We next merged the JANIS data and DPC data by sex, age, date of birth, date of admission, and date of discharge and then stratified the merged data into MSSA and MRSA groups.

Definition of cases

Each *S. aureus* detected from a blood specimen was counted as one case of blood stream infection. To avoid duplication from the same patient, we included only one specimen from the same admission data (i.e., if one patient was admitted twice for *S. aureus* bacteremia in different years, they were counted as two cases).

The criteria for judging the antimicrobial susceptibility of each bacterium were in accordance with the regulations of JANIS, which follows the criteria defined by the Clinical Laboratory Standards Institute (CLSI)[15]. MRSA was defined as *S. aureus* resistant to oxacillin and/or cefoxitin.

Hospitalization cost

We defined hospitalization cost in this study as direct costs from the healthcare payer perspective and then obtained the hospitalization cost of each blood stream infection case through aggregation: 1) prescription cost of drugs; 2) treatment and operation cost;

3) examination cost, including image inspections; 4) accommodation cost; and 5) other expenses.

Statistical analysis

LoS, LoS after submission of a blood culture specimen (LoS-after), total hospitalization cost, hospitalization cost per day, and clinical outcome were compared between the groups after propensity score matching (one-to-one nearest matching, caliper = 0.20) to adjust for the influence of age and sex.[16,17] An absolute standardized mean difference of each covariate (age and sex) above 10% in matched data was regarded as a clinically significant difference, and all such differences were within 10%. In addition, we aggregated the data of all patients admitted to NCGM in the observation period to calculate the LoS and hospitalization cost for all causes of admission.

Two-sided *p* values less than 0.05 were considered statistically significant. All statistical analyses were performed using R version 4.0.3.[18]

Ethics approval

This study was approved by the Ethics Committee of National Center for Global Health and Medicine, Tokyo, Japan (approval number, NCGM-G-003606-00).

Results

Table 1 shows the LoS and hospitalization cost of all patients admitted to NCGM between 2016 and 2020 (i.e., not limited to those with *S. aureus* bacteremia). In total, median hospitalization cost per patient was 5,162 (interquartile range [IQR] 2,745-10,142) USD and median LoS was 7 (IQR 3-15) days. Among all age groups, neonatal patients had the highest hospitalization cost (median 14,432 USD; IQR 8,162-28,311 USD) and the longest LoS (median 13 days; IQR 8-29 days).

(Table 1)

In the population of interest, median LoS was 46 (IQR 28.5-64.5) days in the MSSA group and 66 (IQR 40-91) days in the MRSA group. Median LoS-after was 38 (IQR 25-62.5) days in the MSSA group and 45 (IQR 24-63) days in the MRSA group. Median hospitalization cost and cost per day were respectively 19,823 (IQR 13,764-32,042) USD and 455.6 (IQR 359.2-701.7) USD in the MSSA group and 26,035 (IQR 18,154-47,362) USD and 528.9 (IQR 374.9-647.4) USD in the MRSA group.

The Wilcoxon rank sum test revealed that LoS and hospitalization cost significantly

differed between the groups (p = 0.020 and 0.036, respectively), unlike LoS-after and hospitalization cost per day (p = 0.691 and 0.990, respectively). The case fatality rate was higher in the MRSA group (22/60) than in the MSSA group (9/60) according to Fisher's exact test (p = 0.012). Table 2 shows the results before propensity score matching, and Table 3 shows the results after matching. Figures 1 and 2 are violin plots of LoS and hospitalization cost by strain, respectively.

(Table 2)

(Table 3)

(Figure 1)

(Figure 2)

Figure 3 shows the breakdown of the hospitalization cost for each group.

(Figure 3)

Accommodation cost accounted for more than half of the total hospitalization cost in both groups (59.1% in the MSSA group and 52.6% in the MRSA group). The proportion of the treatment cost was higher in the MRSA group than in the MSSA group (20.6% and 13.7%, respectively).

Discussion

To our knowledge, this is the first study examining the difference in LoS and hospitalization cost between MSSA and MRSA in Japan. In our results, median LoS of all-cause admission was substantially shorter than reported by the OECD.[10] This difference might be due to the calculation methods used. While the OECD reported the average number of days spent by patients in hospital, which is generally measured by dividing the total number of days stayed by all inpatients during a year by the number of admissions or discharges, we used the median LoS of each patient. Therefore, the 16.1 days reported by the OECD would be greatly influenced by outliers (i.e., the extremely long LoS of some patients). Nevertheless, 7 days is longer than the average LoS worldwide (6.6 days) and that in the US (5.5 days).[10]

Notably, the LoS of patients with *S. aureus* bacteremia in Japan is substantially

longer than that in other countries. Cosgrove and colleagues reported that the median LoS for MSSA and MRSA bacteremia in the US was 7 and 9 days, respectively.[19] According to Thampi and colleagues, the median LoS of such patients in Canada was 14 and 22.5 days, respectively.[20] Another study from the Greater Toronto area found a median LoS for *S. aureus* bacteremia of 17 days.[21] In contrast, our results indicated that patients with *S. aureus* bacteremia in Japan are hospitalized for a median 49 days, which is about three times as long as that reported previously in other countries. Even when the data are limited to LoS-after (i.e., LoS after submission of a blood culture), this amounts to twice as long as that reported in other countries. Given these results, it is not difficult to imagine that the disease burden of *S. aureus* bacteremia will be greater in Japan than in other countries.

The cause of the considerable international differences in LoS is unclear but Tiessen and colleagues have obtained some interesting results.[22] Although their study examined the LoS of acute myocardial infarction, they observed a trend similar to that of our results. In their opinion, their results can be explained by nonclinical factors such as professional/cultural norms and differences in healthcare schemes. For instance, acute care hospitals in Japan are generally equipped with a large supply of acute care beds but a small supply of long-term care beds. This combination should theoretically

result in longer acute care stays. In addition, hospital ownership in Japan would also influence the results. Private for-profit organizations perhaps act to fill their capacity, which is higher than that of their counterpart, to maximize revenues. These hypotheses should be carefully examined in future work.

Meanwhile, we should also note that, although there was a difference in total LoS between MSSA and MRSA in our study, there was no substantial difference in LoS-after. This is a markedly different result from that of previous studies.[9,23] Generally speaking, the presence of antibiotic resistance appears to increase LoS and hospitalization costs. This phenomenon is probably related to Japanese healthcare systems and customs. Because residence in a long-term care facility is one of the risk factors of MRSA infection,[24] the longer LoS might be attributable to an increase in novel MRSA bacteremia because patients who tend to stay in the hospital longer also tend to be infected with MRSA. It is possible that the long LoS in Japan is not only unnecessary, but also increases the number of infected cases. Because the LoS-after in Japan is substantially longer than the appropriate duration of antibiotic therapy for *S. aureus* bacteremia,[25] the difference in the recommended duration of antibiotic therapy between MSSA and MRSA does not explain the difference in LoS-after between these strains.

The hospitalization cost of *S. aureus* bacteremia in Japan is neither expensive nor

cheap compared with other developed countries. Thampi and colleagues reported that *S. aureus* bacteremia costs about 12,000 USD per case in Canada.[20] In contrast, it costs more than 37,000 USD in the US.[23] As described above, the LoS in Japan is clearly longer than that in these countries, but the hospitalization cost per day in Japan may be less expensive. In addition, the hospitalization cost per day in Japan is not substantially different between MSSA and MRSA. This result is compatible with that of a recent study from the US,[26] although it contradicts the results of older studies.[19,27–31]

In terms of the clinical outcome of *S. aureus* bacteremia, the case fatality rate of 24.5% in this study is also similar to that in previous studies.[21,32] However, the difference in the case fatality rate between MSSA and MRSA is clear in our study, in contrast to a recent study.[26] This can be attributed to the nature of our data, which are a combination of microbiological test results and patients' claim data and which made it difficult to adjust for confounding factors associated with prognosis.

The present study has several limitations. First, our results are based on data from a single facility. Although our facility is the largest medical center hospital in Japan in terms of infectious diseases, the number of bacteremia cases was limited and biases due to the characteristics of the facility cannot be removed. Therefore, representativeness will be a major concern for our results. Next, as explained in the previous paragraph,

our data do not include the full characteristics of each patient. Although we adjusted for age and sex by propensity score matching, other confounding factors probably affected the results. Third, our claims data capture the cost incurred by the facility. Because the Japanese health insurance system adopts the Diagnosis Procedure Combination/Per-Diem Payment System, the claims data do not precisely reflect the actual cost paid by the government to the facility. In other words, our estimated hospitalization cost might be overestimated if we regard the "healthcare payer" as being the Japanese government.

Despite these limitations, our results provide necessary evidence for international comparisons of the disease burden of *S. aureus* bacteremia. At our hospital in Japan, patients with MRSA bacteremia had longer hospital stays and higher costs than those with MSSA bacteremia. However, the LoS-after and hospitalization cost per day did not differ. Furthermore, the markedly longer LoS in Japan compared with other countries would be of major interest. Further studies of this long LoS in Japan and its reasons based on multicenter, national-level data are necessary because a longer LoS would be a major cause of heavier disease burden for the same disease in Japan compared with other countries. These novel findings might contribute to reduce the burden and medical expenses of *S. aureus* bacteremia in Japan because the LoS in Japan may be

unnecessarily longer than that in other countries and cause additional productivity loss and medical costs.

Acknowledgments

Statements of ethical approval: This study was approved by the Ethics Committee of National Center for Global Health and Medicine, Tokyo, Japan (approval number, NCGM-G-003606-00).

Funding: This study was supported by a Ministry of Health, Labour and Welfare (MHLW) research grant of Japan (20HA2003).

Competing interests: We declare no competing interests.

Data sharing: Data used in this study are available from the corresponding author upon reasonable request.

Contributors: ST and NO conceived the study. JY collected and managed the data. ST performed statistical analyses and drafted the first draft of the manuscript. NM, JY, and

NO critically reviewed the manuscript and all authors approved the final version of the manuscript.

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Table 1. Cost and length of stay of all patients in the National Center for Global Health and Medicine, 2016-2020

Age group	Cost (USD*)	Cost (JPY)	Length of stay (days)
Neonates	14432 (8162-28311)	1587565 (897835-3114155)	13 (8-29)
Infants	4553 (3446-6390)	500870 (379080-702890)	6 (4-8)
1-14 years	5145 (3605-6921)	566000 (396555-761280)	5 (3-7)
15-64 years	4808 (2529-9143)	528882 (278230-1005783)	7 (3-13)
65-89 years	5219 (2696-11235)	574105 (296603-1235814)	8 (2-17)
90 years and older	6969 (3706-13010)	766628 (407668-1431061)	12 (5-25)
Total	5162 (2745-10142)	567800 (301936-1115629)	7 (3-15)

Values are shown as the median (interquartile range).

*1 USD = 110 JPY.

Table 2. Length of stay, hospitalization cost, and in-hospital mortality of patients with *S. aureus* bacteremia in the National Center for Global Health and Medicine, 2016-2020

	MSSA (n=84)	MRSA (n=63)	Total (n=147)
Age	**72 (50-82)**	**76 (64-89)**	**74 (58-85)**
Male sex	**44 (52.4)**	**35 (55.6)**	**79 (53.7)**
LoS (days)	**40 (27.5-64.5)**	**66 (37.5-87)**	**49 (29-76)**
LoS-after (days)*	**32 (22-59.5)**	**43 (23-62)**	**32 (17-56)**
Hospitalization cost (USD)**	**20884 (13880-33951)**	**27798 (18252-47543)**	**22902 (15699-43330)**
Hospitalization cost (JPY)	**2297240 (1526856-3734595)**	**3057807 (2007727-5229778)**	**2519214 (1726905-4766352)**
Hospitalization cost per day (USD)**	**401 (150-1111)**	**496 (231-1215)**	**488 (374-719)**
Hospitalization cost per day (JPY)	**44085 (16527-122191)**	**54518 (25374-133648)**	**53651 (41181-79102)**
In-hospital death	**12 (14.3)**	**24 (38.1)**	**36 (24.5)**

MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant

Staphylococcus aureus; LoS, length of stay.

Values are shown as the median (interquartile range) or number (percentage).

*Length of stay after blood culture submission.

**1 USD = 110 JPY.

Table 3. Comparison of length of stay, hospitalization cost, and in-hospital mortality of MSSA and MRSA bacteremia after propensity score matching

	MSSA (n=60)	MRSA (n=60)	*p*-value[†]
Age	**76 (66-83)**	**76.5 (65.5-89)**	**0.303**
Male sex	**33 (55.0)**	**32 (53.3)**	**1.0**
LoS (days)	**46 (28.5-64.5)**	**66 (40-91)**	**0.020**
LoS-after (days)[*]	**38 (25-62.5)**	**45 (24-63)**	**0.691**
Hospitalization cost (USD)[**]	**19823 (13764-32042)**	**26035 (18154-47362)**	**0.036**
Hospitalization cost (JPY)	**2180493 (1514005-3524635)**	**2863872 (1996922-5209858)**	**0.036**
Hospitalization cost per day (USD)[**]	**456 (359-702)**	**529 (375-647)**	**0.990**
Hospitalization cost per day (JPY)	**50113 (39516-77191)**	**58174 (41238-71212)**	**0.990**
In-hospital death	**9 (15.0)**	**22 (36.7)**	**0.012**

MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; LoS, length of stay.

Values are shown as median (interquartile range) or an absolute number (percentage).

*Length of stay after blood culture submission.

**1 USD = 110 JPY.

†Mann-Whitney test for continuous variables and Fischer's exact test for binary variables.

Figure legends

Figure 1. Length of stay after blood culture submission by strain

MSSA, methicillin-susceptible *Staphylococcus aureus*; RF, methicillin-resistant *Staphylococcus aureus*.

Figure 2. Hospitalization cost per day by strain

MSSA, methicillin-susceptible *Staphylococcus aureus*; RF, methicillin-resistant *Staphylococcus aureus*.

Figure 3. Breakdown of the total hospitalization cost from 2016 to 2020

The horizontal axis represents the accumulated hospitalization cost during the study period.

Figure1

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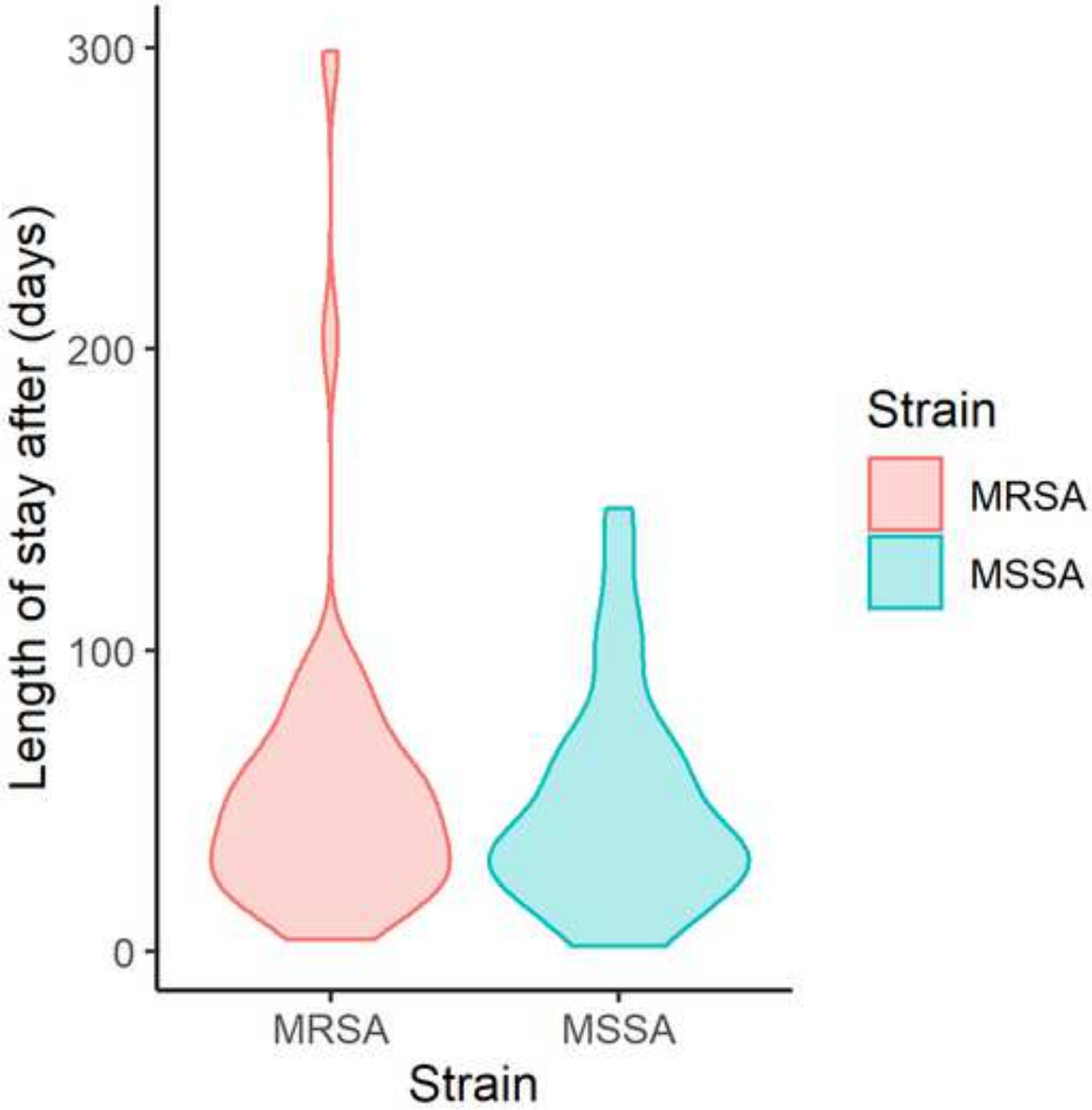

Figure2

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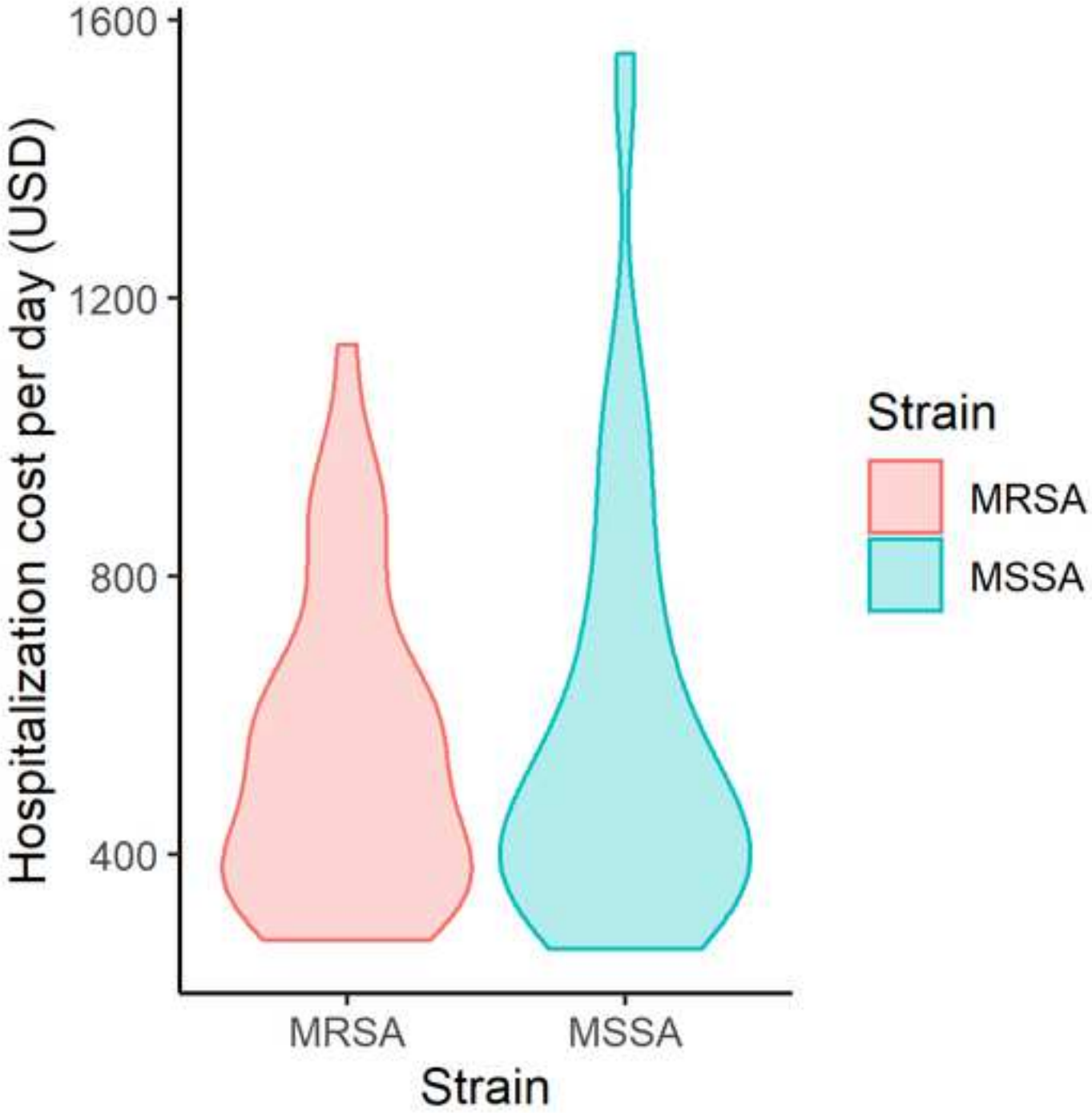

Figure3

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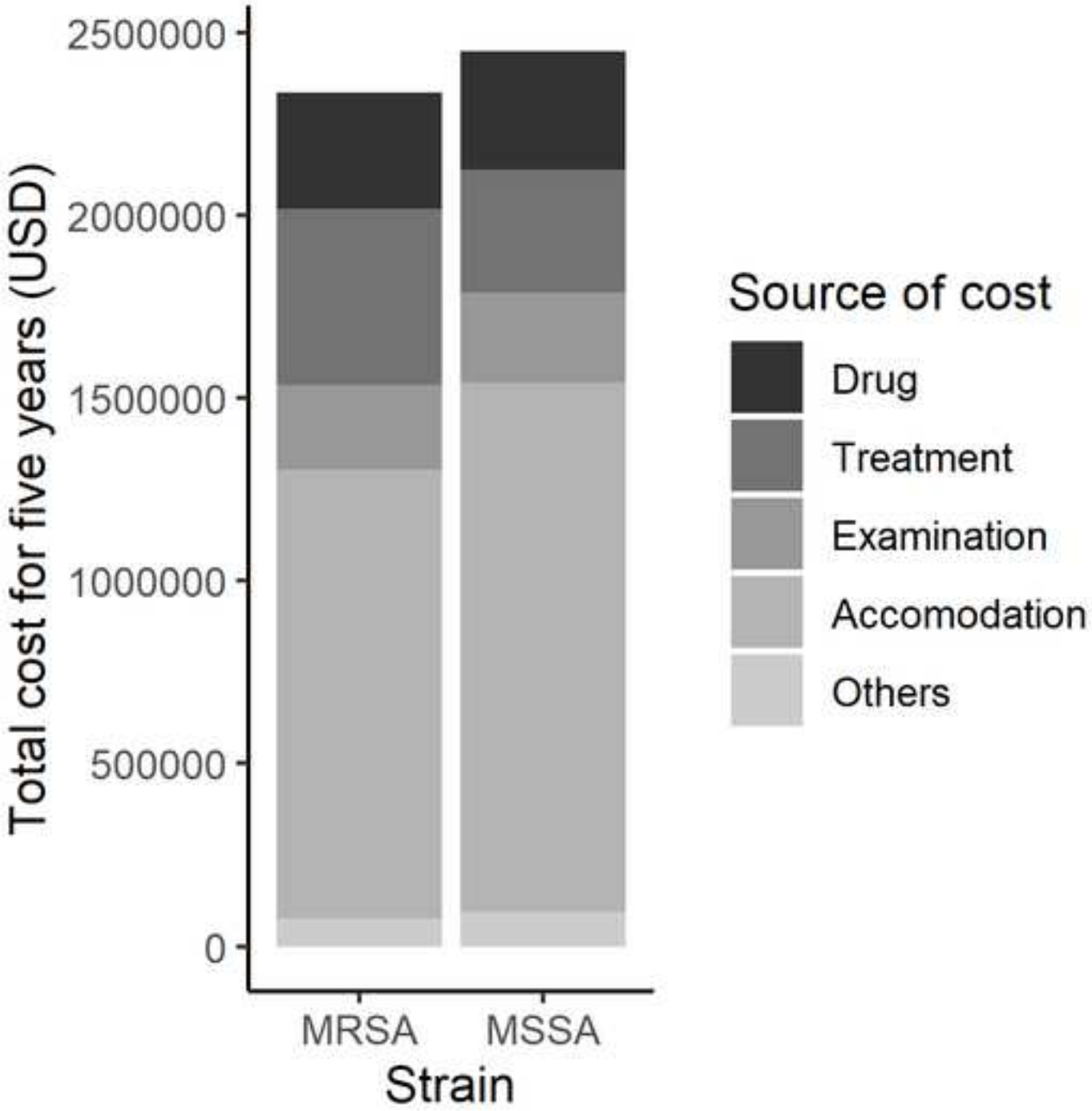

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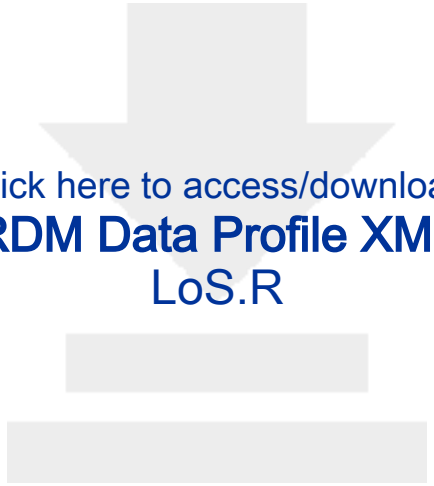

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