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1 **Code-sharing in Cost-of-illness Calculations: An Application to**
2 **Antibiotic-Resistant Bloodstream Infections**

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13 **Key words: Cost, length of stay, antibiotic resistance, code sharing, Staphylococcus aureus**

14 **Abstract**

15 **Background:** More data-driven evidence is needed on the cost of antibiotic resistance. Both Japan
16 and England have large surveillance and administrative datasets. Code sharing of costing models
17 enables reduced duplication of effort in research. **Objective**: To estimate the burden of antibiotic-
18 resistant *Staphylococcus aureus* bloodstream infections in Japan, utilizing code that was written to
19 estimate the hospital burden of antibiotic-resistant *Escherichia coli* bloodstream infections in
20 England. Additionally, the process in which the code-sharing and application was performed is
21 detailed, in order to aid future such use of code-sharing in health economics. **Methods:** National
22 administrative data sources were linked with voluntary surveillance data within the Japan case study.
23 R software code, which created multistate models to estimate the excess length of stay associated
24 with different exposures of interest, was adapted from previous use and run on this dataset. Unit costs
25 were applied to estimate healthcare system burden in 2017 international dollars (I$). **Results:** Clear
26 supporting documentation alongside open-access code, licensing and formal communication
27 channels, helped the re-application of costing code from the English setting within the Japanese
28 setting. From the Japanese hospital perspective, it was estimated that there was an excessis a cost of
29 I$6,3927,000 per *S. aureus* bloodstream infection (compared to no infection), whilst oxacillin
30 resistance was associated with an additional excess cost of I$8,15510,000. **Conclusions:** *S. aureus*
31 resistance profiles other than methicillin may substantially impact hospital costs. The sharing of
32 costing models within the field of antibiotic resistance is a feasible way to increase burden estimates
33 efficiently, allowing for decision makers (with appropriate data available) to gain rapid cost-of-illness
34 estimates.

35

36

1 Introduction

38 Health economics and outcomes research related to infectious disease often needs to take into
39 account unique factors that can lead to increasingly complex statistical and economic methodology
40 [1].[1] Cost-effectiveness models of interventions related to infectious disease should (generally)
41 account for infectious disease transmission dynamics [2],[2] whilst costing studies related to
42 healthcare-associated infections should account for factors such as time dependency bias. Time
43 dependency bias describes a bias that arises when the time of infection isn't fully taken into account
44 when attributing hospital costs to a condition [1]. For example, if a full hospital stay was attributed to
45 a methicillin-resistant *Staphylococcus aureus* (MRSA) infection, but the patient only contracted
46 MRSA after being in hospital for ten days, you are wrongly attributing ten days of hospital costs to
47 that MRSA infection. Estimating the cost of such infections accurately is key to ensuring robust cost
48 parameters are utilized in cost-effectiveness analyses. Current literature has focused on estimating the
49 impact of methicillin resistance, as opposed to also estimating the burden of other antibiotic
50 resistance profiles relative to *S. aureus* infections [3, 4]. [3, 4]

51 Accounting for time dependency bias, whilst also adjusting for other key factors like patient age
52 and/or comorbidity, requires the use of models such as sub-distribution hazard models[5] or adjusted
53 multistate models.[6] In order to apply such techniques, a flexible data analysis software environment
54 is needed.[6] Similarly, building cost-effectiveness models which account for transmission of
55 infections, potentially between patient populations and environments, requires more flexibility in the
56 model building process. These factors have played a part in the increase in the use of R, an open-
57 source software environment that allows users to build complex health economics models directly or
58 easily adapt the previous work of other users [7–9].[7–9]

59 There are two main ways in which health economists can utilize and build upon the work of previous
60 colleagues when constructing models in R; the first is through downloading "packages" directly from
61 the host of R code ('The Comprehensive R Archive Network') [10],[10] the second is downloading
62 available code from code-sharing sites [11].[11] Packages are, in essence, downloadable scripts of
63 code performing defined functions (such as de-duplicating datasets), with documentation available
64 online explaining the usability of such functions [10]. Code shared via open-access, code-sharing
65 websites can provide the same service, however can be more informal. Additionally, researchers may
66 choose to share code on such sites not as a way to share defined 'reproducible' functions for future
67 analyses, but rather to be transparent in the data analysis or modelling procedures used in relevant
68 published manuscripts.

69 The practice of using code-sharing sites for collaboration and transparency should, theoretically,
70 reduce time spent on duplication of basic code, increase efficiency in building health economic
71 models within the field of infectious disease and increase robustness of such models (due to potential
72 critique through increased transparency). As the use of R for health economic models continues to
73 grow, and with the addition of health economics package collations pages such as "Health
74 Economics R Packages" available online [12, 13] being compiled within GitHub [12], we wanted to
75 show the potential advantage of code sharing in health economics applied to infectious disease.

76 Both Japan and England have large, infection surveillance and hospital administrative data sets [9,
77 14]. Therefore, this short commentary piecereport discusses the process and subsequent results of an
78 international collaboration in which Japan-based health economists estimated the hospital cost of

2

79 bloodstream infections using England-based equivalents' R code [9], shared through GitHub [15].
80 The objectives of this brief report were to; (i) describe the code sharing process used to estimate cost
81 of infections across two different, high-income country settings; and (ii) describe the top-line results
82 of the analysis in Japan for a range of antibiotic resistance profiles.

83 **2   Methods**

84 **2.1   Process Methodology**

85 Research was previously conducted to estimate the health and cost burden of antibiotic-resistant and
86 antibiotic-susceptible *Escherichia coli* bloodstream infections in the English secondary care setting,
87 using national administrative and surveillance datasets [9], this will be referred to as 'the English
88 study'. As some of these infections occur during a patient's hospital stay, time dependency bias had
89 to be taken into account, and as such multistate models were built to estimate excess length of
90 hospital stay (LoS) associated with *E. coli* bloodstream infections [1].
91
92 Multistate models estimate LoS as a function of (i) the number of people within each health state
93 (such as number of patients in the infected state) and (ii) the number of transitions between health
94 states (such as number of patients moving from infected to discharged) for specified time intervals
95 (such as days) [16]. The English study utilised R software to construct these models, specifically
96 using the "etm" and the "mvna" packages [17, 18]. As these R packages allowed for a maximum of
97 one exposed group and non-exposed group to be compared at a time, models were constructed that
98 first compared infected with non-infected patients, and then compared antibiotic resistant infections
99 with antibiotic susceptible/intermediate infections for different antibiotics of interest [9]. ~~Detailed~~
100 ~~methodology can be found within the related publication [9].~~
101
102 ~~The English study utilised R software, and R packages such as 'survival' [16], to clean and analyse~~
103 ~~the data.~~
104 The related code was subsequently deposited (open-access) to GitHub [15]. The relevant GitHub
105 repository included the R scripts used within the data analysis on the English datasets, a data
106 dictionary detailing the key variable definitions and a codebook which describes what the R scripts
107 intend to do. This code was then downloaded by colleagues within the Japan study, adapted where
108 needed, and utilised on Japanese hospital data to estimate the cost burden of antibiotic-resistant
109 *Staphylococcus aureus* bloodstream infections. This will be referred to as 'the Japanese study'.
110
111 To begin the code application within the Japanese study, the code was downloaded and tested by
112 health economists. Subsequently a meeting was held with colleagues across the partnering
113 institutions to go through the code and its application within the Japanese study. Whilst a face-to-face
114 (or virtual) meeting is not a necessity, the authors found it an efficient way of dealing with nuances
115 of the code application to different data sources.
116

117 **2.2   The Japanese Study**

118 Copies of datasets from participating hospitals of The Japan Nosocomial Infections Surveillance
119 (JANIS) system, a Japanese governmental surveillance system, were utilised as the data source for
120 this analysis. JANIS is a voluntary surveillance system which covers around 30 % of Japanese
121 hospitals [19]. These bacterial surveillance data collected from hospitals (JANIS dataset) were linked
122 to administrative data; Diagnosis Procedure Combination (DPC) data, also collected from these

123   hospitals to obtain admission, discharge and patient data (JANIS-DPC database [4]). The Ethics
124   Committee, Graduate School of Medicine, Kyoto University approved the study (reference - R0577).
125
126   Acute care hospitals (most of which are educational hospitals) were included in this analysis,
127   including private, public, and university hospital throughout Japan. This is a similar setting to the
128   English study, which was based in acute care National Health Service (Foundation) Trusts. Adult,
129   patient data on *S. aureus* bloodstream infections were extracted from the JANIS dataset between
130   April 2014 and March 2016., This represent~~ed~~ing two Japanese, fiscal years. Definitions of antibiotic
131   resistance were in line with the JANIS data definition, which is line with governmental guidance
132   [20]. Antibiotic resistance impact was investigated in relation ~~relating~~ to first-generation
133   cephalosporin, carbapenem, gentamicin, fluroquinolones and penicillin (including methicillin and
134   oxacillin), as these are important classes with resistance case numbers greater than 1,000.
135   Additionally, oxacillin was selected by the Japanese study as a key antibiotic to test individually.
136   'Not-tested' was included in our non-exposed controls, allowing for use of all available data and
137   consistency with the English study [9].~~, this may lead to conservative results as bloodstream~~
138   ~~infections resistant to exposures of interest (but not tested) could be wrongly placed within the non-~~
139   ~~exposed category, however this is consistent with the English study.~~
140
141   Multistate models were ~~then~~ used to estimate the excess LoS of *S. aureus* bloodstream infections, as
142   done in previous analyses [3, 8, 9]. Figure 1 depicts the structure of these. Cumulative transition
143   hazards representing the movement between states were calculated using the data provided. These
144   were then used to estimate 'expected LoS' on each day (t) [16, 21]. These estimates for each day (e.g.
145   expected LoS for infected patients minus expected LoS for non-infected patients on t=2) are then
146   averaged across all days of the study period (weighted by frequency of events) to get an estimate of
147   average excess LoS [7]. Artificial censoring was used to reduce the impact of outliers on multistate
148   model results [3]. The artificial censoring time was moved from 45 days (from the English study) to
149   90 days (for the Japanese study), due to the longer average inpatient LoS for Japanese hospital
150   patients. For example, a recent OECD report has stated that average LoS for acute care in Japan in
151   2017 (16.5 days) was much higher than in the UK (6.9 days respectively) [22]. ~~[4, 9].~~
152
153   To estimate costs from the healthcare system perspective, the unit cost of an excess bed day was
154   applied to excess LoS estimates. The most applicable cost found was~~-~~ the World Health Organisation
155   (WHO) estimation of a cost per inpatient bed day for Japan [514.26 in 2010 international dollars
156   (I$)], which was estimated as part of the WHO-CHOICE estimates of cost for inpatient and
157   outpatient health service delivery [23] ~~an estimate of $649 (USD) per marginal bed day, taken from a~~
158   ~~report focusing on estimating the cost of healthcare-associated infections in Asia-Pacific Economic~~
159   ~~Cooperation countries [20].~~ This 201~~0~~3 cost was converted to Japanese Yen using purchasing power
160   parity (PPP) [24] ~~[23]~~, inflated to 2017 costs using ~~the consumer price indices~~the Gross Domestic
161   Product implicit price deflator~~-~~[25]~~[24]~~, then converted back to I$ ~~international dollars (I$)~~ using PPP
162   [24]~~[25].~~, ~~to give~~This gave an~~ an~~ estimate of $551~~688~~ per day (2017 I$). This process of cost
163   conversion is in line with guidance that has been previously published [26, 27].

164   Descriptive statistics were summarized, with median and interquartile ranges used for continuous
165   variables, and proportions (represented by percentages) used for categorical variables.

3   Results

3.1   Process Results

168   Researchers from the English study cleaned the R script code, wrote a corresponding data dictionary
169   and relevant codebook to explain the R scripts. These were then uploaded to a code sharing website
170   [15]. Researchers in the Japanese study downloaded this code and began to adapt according to their
171   exposures of interest and the data available. For example, variable names within the cleaning code of
172   the English study needed to be adapted to match the variables names in the linked JANIS-DPC
173   database. Colleagues leading the Japanese study were familiar with the datasets, enabling an
174   understanding of how to adapt data formats to fit into the coded structure fairly quickly. Harmonizing
175   data structures is key in applying code that was built for other analyses, and determination as to
176   whether key variables are present in the application dataset is needed as a first step.

177   R scripts that created time-dependent data-sets (i.e. accounted for the time between admission and
178   infection for hospital-onset infections), created multistate models to estimate excess LoS were
179   downloaded, adapted and run in the Japanese study. Subsequently, licensing information for the code
180   was added to the English study code [15], and should be added in future coding uploads of this
181   nature, to reduce legal ambiguity on the source code [28].

182   Clear annotation of code, and consistent labelling of particular processes was noted as highly useful
183   for the Japanese study when utilizing the English study code. Throughout the data cleaning and
184   analyses, the data dictionary and codebook were noted as being instrumental in aiding the adaptation
185   of variable names and R code processes to fit the Japanese data.

186   This process led to time-efficient cost estimates for *S. aureus* being available, with reduced time
187   spent on initial data cleaning and basic analysis coding for the Japanese study.

188 **3.2   The Japanese Study Results**

189   4,017 *S. aureus* bloodstream infection inpatient spells were included in the analysis. To estimate the
190   excess LoS of these infections, these spells were compared to 1,215,119 patient spells which were
191   not related to *S. aureus* bloodstream infections. Descriptive statistics are presented in Table 1 ~~below~~,
192   in which you can see over 25% of exposed patient spells resulted in in-hospital mortality, compared
193   to less than 5% in the non-exposed group.

194   Initial results showed that *S. aureus* bloodstream infections, when accounting for time dependency
195   alone, were associated with an excess length of hospital stay by an average of 11.6 days. This
196   increase in hospital stay translated into an excess cost ~~Japanese hospitals~~of ~~over~~ I$6,392 ~~7,000~~ per
197   infection, when applying the unit cost of a bed day (as described in the methods section). ~~(Table 2).~~
198   ~~Additionally, an *S. aureus* bloodstream infection resistant due to oxacillin was over $10,000 more~~
199   ~~costly (per infection) than its oxacillin-susceptible equivalent.~~ Resistance to all tested antibiotics was
200   associated with an excess LoS of over 10 days. The resistance exposures that had the largest absolute
201   association~~effect~~ were oxacillin (14.8 days), first generation cephalosporin (13.7 days) and
202   carbapenem (13.7 days) resistant exposures (comparative to their relevant ~~susceptible~~ non-exposed
203   cases respectively). The translation of this into estimates of monetary impact can be seen in Figure 2.
204   The range of the excess cost per infection associated with resistance was estimated to be from
205   I$5,675 (for gentamicin resistance) to I$8,155 (for oxacillin resistance).

206 **4   Discussion**

207   This work highlights the potential for code sharing to reduce research burden in health economics
208   across international settings. This report details key things to consider in the sharing of costing
209   models, namely; discussing the appropriateness of the data structures and variables initially, ensuring

210   appropriate licensing is in place and being upheld, providing and using in-depth supporting
211   document, and (even if a formal collaboration is not feasible) communication between the code's
212   original authors and those applying code is necessary to reduce mistakes in code interpretation and/or
213   application. Code that was written to analyze English hospital data[9, 15], was used directly on
214   Japanese hospital data, producing time-efficient cost estimates relating to *S. aureus* bloodstream
215   infections. This suggests such code (which is currently available open-access [15]) may be useful in
216   other healthcare systems in estimating the impact of antibiotic resistance.

217   It was estimated that *S. aureus* bloodstream infections was associated with ~~led to~~ patients staying in
218   hospital for an extra 12 days on average. Antibiotic resistance was estimated to be associated with an
219   excess LoS for tested exposure groups by between 10 and 15 days. Previous research within the
220   Japanese setting that estimated the burden of MRSA, based on antibiotics prescribed, estimated an
221   excess LoS of 51 (95% CI; 30–88) days for those on 'anti-MRSA'-antibiotics, 16 (9–30) days for
222   those on 'non-anti-MRSA' antibiotics and 6 (3–12) days for non-infected patients [4]. However, the
223   case definitions were different so it is difficult to make direct comparisons to our results.

224   Estimates of excess length of stay from resistance-related exposures of interest ranged from around
225   10 to 15 days in the Japan case, much higher than those estimated in the English study (ranging from
226   roughly 0.5 to 1.5 days). However, this is in line with the difference between general differences seen
227   in hospital LoS across the two studies, with the non-infected controls for Japan and England having a
228   median ~~length of stay~~LoS of 8 and 0.5 days respectively [4, 9]. Additionally, as highlighted in the
229   methods, this is in line with previous international comparisons of inpatient LoS [22]. Cited potential
230   reasons for such international variation include differences in bed supplies and differences in hospital
231   payment systems [22].

232   ~~Previous research within the Japanese setting that estimated the burden of MRSA, based on~~
233   ~~antibiotics prescribed, estimated that the MRSA group had an excess LoS of 51 (95% CI; 30–88)~~
234   ~~days, the 16 (9–30) days for those on non-MRSA antibiotics and 6 (3–12) days for non-infected~~
235   ~~patients.[4] Though the case definitions are slightly different our descriptive statistics align with~~
236   ~~these estimates.~~

237   *Strengths and Limitations*

238   Getting rapid, initial results in estimating the burden of antimicrobial-resistant infections, as in the
239   case presented here, can be important for deciding treatment policy on a regional or local level. The
240   excess LoS and cost results presented in this report provide initial estimates of the absolute effects
241   associated with a variety of antibiotic exposures. These estimates highlight the need for future
242   primary and secondary research in *S. aureus* bloodstream infections to investigate the impact of
243   different antibiotic susceptibility profiles (such as oxacillin), not just methicillin, on patient
244   outcomes.

245   The costs are derived using ~~excess length of stay results reported are estimates adjusting for time~~
246   ~~dependency alone, and are costed using~~ an ~~regional reference~~ excess bed day cost (so do not account
247   for further drug or other associated medical costs). Though this is in line with previous literature [9,
248   29]. ~~.[9, 25]~~ The cost of a bed-day was taken from WHO-CHOICE, which is a modelled cost
249   estimated that was based on a global analysis [23]. However, other, usable estimates were not
250   readily-available within the literature for this setting. Another bias that may result in conservative
251   estimates is that bloodstream infections resistant to exposures of interest (but not tested) could be
252   wrongly placed within the non-exposed category. However, this was preferred to dropping non-tested

253 cases or grouping them with the exposed category, the latter of which could lead to overly generous
254 estimates in terms of resistance-associated excess LoS.

255 Uncertainty has not been estimated through the application of techniques such as bootstrap sampling,
256 however, such processes do require more time and computing resources. Statistical significance is
257 therefore not determined for the outcomes presented in this brief research report. Additionally, the
258 underlying excess LoS results reported are estimates adjusting for time dependency alone. Therefore,
259 for more robust 'excess cost' estimates in the future, patient covariates should be taken into account
260 and uncertainty intervals calculated using similar methods as applied in the English study [9].
261 Though limited by the aforementioned factors, the estimates presented here are important regarding
262 Japanese health policy, with the current and potential future burden *S. aureus* bloodstream infections
263 being a major cause for concern in this setting [14].[12]

264 Processes such as the one described in this report could reduce the 'cost of information' when
265 analyzing the value of additional information in health economic evaluations. Though seemingly
266 simple, this process of code sharing and transparency between health economists could lead to more
267 efficient research, more cost evidence, cost-effectiveness evidence and therefore, theoretically, more
268 efficient resource allocation decisions. This is particularly relevant in the field of antimicrobial
269 resistance. There have been calls for more robust epidemiological and health economic estimates
270 utilizing data [30].[26] The sharing of code amongst health economists within this field, and in health
271 economics in general, could help reduce research waste and increase collaboration. The call for open
272 science can be extended to related manuscripts; with an appeal for open-access versions of cost-of-
273 illness manuscripts which describe in more detail the methods and results, for example through
274 author or institutional websites (if not an open-access article in itself).

275 **5   Conclusion**

276 Antibiotic resistance (as defined across different antibiotic classes), on average, was associated with
277 results in an additional healthcare system cost of between I$5,6757,000 and I$8,15510,000 per *S.*
278 *aureus* bloodstream infection in Japan. These estimates were calculated using reduced resources due
279 to the code-sharing practices described in this report., and can be utilized by relevant policy makers
280 in budget priority setting. Such estimates can be used in future budget and research priority setting,
281 whilst such code-sharing practices can reduce future research burden.

282 **6   Conflict of Interest**

283 The authors declare that the research was conducted in the absence of any commercial or financial
284 relationships that could be construed as a potential conflict of interest.

285 **7   Author Contributions**

286 All authors aided were involved in the initial conceptual idea for the study through attendance of
287 anthe initial collaboration meeting. All authors were involved in drafting the manuscript. KY and SK
288 conducted the analysis and NN wrote the original code adapted by KY. NN wrote the first
289 manuscript draft. NN, KY and SK wrote up the results and interpreted the initial results. RA, MI, SM
290 provided results interpretation guidance. YI provided acquisition of data used. SM and MI provided
291 administrative support for this study. YI, EC-S, MI, SK, RA, AH were involved in obtaining funding
292 for this study and for time used within this study. AH, YI and RA provided supervision for this
293 project.

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414 **Table 1. Descriptive Statistics of Exposed and Non-Exposed Patient Hospital Spells**

415 Abbreviations: BSI – bloodstream infection, IQR – interquartile range, SD – standard deviation

Descriptor	Characteristic (measure)	Non-"Staphylococcus aureus BSI"	Staphylococcus aureus BSI
Sample Size~~Total~~	Number of Hospital Spells	1,215,119	4,017
Gender	Male	575,615 (47.4%)	1,586 (39.5%)
Median Age	Median age in years (IQR)	70 (58 - 79)	77 (66 – 85)
Elixhauser Comorbidity Index	Mean (SD)	5 (6.63)	7.64 (7.06)
Average length of stay	Median days in hospital (IQR)	8 (4 – 17)	34 (16 – 63)
Mortality	In-Hospital Mortality (%)	4.8%	27.6%

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417 **Table 2. Excess Length of Stay ~~and Cost~~ Estimates for *Staphylococcus aureus* Bloodstream**
418 **Infections according to Resistance Profiles**

419 All estimates adjust for time dependency only. Abbreviations: BSI - bloodstream infection, CI –
420 confidence interval, n – number of spells relating to that exposure/non-exposure, SA –
421 *Staphylococcus aureus*.

Exposure Group (number of cases)	Non-exposure Group (number of cases)	Excess Length of Stay (in Days)
Staphylococcus aureus (SA) BSI (n=4,017)	Non-Infected Controls (n=1,215,119)	11.6
SA BSI resistant to 1st generation Cephalosporins (n=1,393)	SA BSI not resistant to 1st generation Cephalosporins (n= 2,624; 2,283 susceptible & 341 not tested)	13.7
SA BSI resistant to Carbapenems (n=1,362)	SA BSI not resistant to Carbapenems (n= 2,655, 2,340 susceptible & 315 not tested)	13.7
SA BSI resistant to Gentamicin (n=1,334)	SA BSI not resistant to Gentamicin (n= 2,683, 2,505 susceptible & 178 not tested)	10.3
SA BSI resistant to Fluroquinolones (n=1,627)	SA BSI not resistant to Fluroquinolones (n= 2,390, 2,273 susceptible and 117 not tested)	11.6
SA BSI resistant to Penicillins (n=2,751)	SA BSI not resistant to Penicillin (n = 1,266, 1,250 susceptible and 16 not tested)	12.9
SA BSI resistant to Oxacillin (n=1,186)	SA BSI not resistant to Oxacillin (n=2,831, 1,633 susceptible & 1,198 not tested)	14.8

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Figure 1. Multistate Models to Estimate Excess Length of Stay

Boxes represent possible health states (green boxes representing *Staphylococcus aureus* states) and arrows represent potential transitions between states. For (A) the exposure group is *Staphylococcus aureus* bloodstream infections. For (B) a separate model was constructed for each antibiotic exposure group of interest, whereby healthcare-associated infections entered the model at time of infection. "Not antibiotic resistant" included susceptible and not tested (as defined by the data source used).

[Insert Figure 1A and Figure 1B here]

Figure 2. Excess Hospital Cost associated with Antibiotic Resistance in *Staphylococcus aureus* Bloodstream Infections

Costs presented are in 2017 International Dollars (I$). Costs presented are those associated with excess length of stay. The exposure groups are patients with *S. aureus* bloodstream infections that are resistant to the stated antibiotic groups. These are compared to patients with *S. aureus* bloodstream infections that are not resistant to the respective antibiotic groups. Note the penicillin category includes methicillin and oxacillin. Oxacillin was selected by the Japanese study as a key antibiotic to test individually in addition to this. Ordering was based on ascending cost estimates.

[Insert Figure 2 here]