Author's response to reviews

Title: Long term care facilities are more important than hospitals in the transmission of methicillin-resistant Staphylococcus aureus

Authors:

Vincent CC Cheng (vcccheng@hkucc.hku.hk)
Josepha WM Tai (taiwm@ha.org.hk)
Zoie SY Wong (zoiewong@cityu.edu.hk)
Jonathan HK Chen (jonchk@hku.hk)
Kris BQ Pan (baoqipan@cityu.edu.hk)
YZ Hai (yizhenhai2@student.cityu.edu.hk)
WC Ng (ngwc1@ha.org.hk)
Denise MK Chow (mkchow@hku.hk)
Miranda CY Yau (mirandayaucy@yahoo.com.hk)
Jasper FW Chan (jaspchan@gmail.com)
Sally CY Wong (scywong@gmail.com)
Herman Tse (htse@hkucc.hku.hk)
Sophia SC Chan (nssophia@hkucc.hku)
KL Tsui (kltsui@cityu.edu.hk)
Felix HW Chan (fchan@ha.org.hk)
PL Ho (plho@hkucc.hku.hk)
KY Yuen (kyyuen@hkucc.hku)

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Author's response to reviews: see over
Dear Dr Philippa Harris
Executive Editor
BMC-series Journals

Long term care facilities are more important than hospitals in the transmission of methicillin-resistant Staphylococcus aureus

Thank you very much for revising our manuscript.

We have made a point to point response to all the questions raised by Reviewer 1 and the Editorial board. The manuscript has been revised. We appreciate your guidance in improving the description of the methodology. With reference to the STROBE guidelines, which is kindly provided by the Editorial board, we have extensively modified our methodology as suggested. A new figure (Figure 2 in the revised submission) has been added in the revised manuscript in order to define the workflow in this study.

We hope that the revised manuscript is acceptable after our extensive revision.

We look forward to the prompt decision from the Editor.

Thank you for your kind attention.

Dr. Kwok-Yung Yuen
Department of Microbiology
The University of Hong Kong
Corresponding author
Point-by-Point Response

Reviewer 1 comments:

1. Unfortunately, I still have major issues with this paper. Although some areas of the paper have been clarified, this study still appears to lack methodological rigor which I deem necessary to warrant publication. I believe the question the paper addresses is important, but while the other reviewer felt that this article was important, I disagree because of these methodological problems. Clearly the authors have done a lot of work, but even their primary outcome of interest is still vague to me because of the description of their methods.

Answer:

We appreciate the reviewer’s comment. The Editor has kindly provided us the STROBE guidelines for reports of studies as reference to address many of the concern raised by Reviewer 1. (http://www.strobe-statement.org/index.php?id=available-checklists) According to the checklist in the guideline, we have extensively modified our methodology as suggested.

According to the checklist, it is required to have a “Study design” to present the key elements of study design early in the paper. Therefore, we have added a paragraph of “Study design” in page 4 Line 3-7 in our revised manuscript as follow:

Study design (Page 4 Line 3-7)
“This study began by comparing the prevalence and risk factors of MRSA colonization between LTCFs and hospitals. Then, the incidence of MRSA transmission per 1000-colonization-days among the resident during their stay in LTCFs and hospital were compared. The transmission of MRSA was analyzed by spa typing, and the relationship between MRSA prevalence and living area per LTCF resident was estimated in this study.”

According to the checklist, it is required to have a “Setting” paragraph to describe the setting, location, and relevant dates, including period of recruitment, exposure, follow-up, and data collection. Therefore, we have revised our manuscript to fulfill the requirement as follow:

Setting (Page 4 Line 12-23)
“LTCFs is a collective term for all long term nursing facilities that provide daily nursing care for their residents including the use of feeding tubes, urinary catheters and other medical devices. The hospital network of our healthcare region included a tertiary referral university-affiliated acute
hospital with 1600 beds, 3 extended-care hospitals with a total of 1600 beds, and 1 pediatric hospital. Patients from LTCFs within our healthcare region would be admitted to the acute hospital for management. Once stabilized, patients would either be discharged to their original LTCFs or transferred to one of the 3 extended-care hospitals within the regional hospital network before returning to the LTCFs. Community geriatric assessment team, comprising of geriatricians, nurses and allied health professionals, would provide regular on-site visits to the LTCFs within our healthcare region for comprehensive medical follow-up and recommendations on infection control measures.”

Location   (Page 4 Line 10-12)
“A prospective study was conducted from 1 July to 31 December 2011 to determine the prevalence and acquisition of MRSA among LTCFs and their network hospitals in the Hong Kong West Cluster, which served a population of 0.53 million.”

Relevant dates   (Page 4 Line 10-12)
“A prospective study was conducted from 1 July to 31 December 2011 to determine the prevalence and acquisition of MRSA among LTCFs and their network hospitals in the Hong Kong West Cluster, which served a population of 0.53 million.”

Period of recruitment
Staff recruitment   (Page 5 Line 12-15)
“Student nurses were recruited for specimen collection at LTCFs and hospital admission wards between 1 July and 31 August 2011. They were trained by infection control nurses on the techniques in taking nasal swabs according to a standard protocol as previously described [19].”

Specimen recruitment
(Page 6 Line 10-12)
“To obtain the number of MRSA carriers among the LTCF residents being hospitalized, MRSA screening from nasal swabs were taken within 24 hours after the first admission of the LTCFs subgroup in our acute hospital.”

(Page 5 Line 20- Page 6 Line 1)
“To determine the differences between patients with probable LTCF-acquired MRSA and probable hospital-acquired MRSA, patients were classified into “LTCF subgroup” and “hospital subgroup” for further analysis. LTCF residents who had no history of hospitalization in the past 12 months are classified as ‘LTCFs subgroup’, while “hospital subgroup” consisted of
Follow-up (Page 8 Line 1-3)
“Swab specimens collected from study subjects were delivered to the laboratory immediately for inoculation on MRSA chromID culture media (bioMérieux), which was incubated aerobically at 35°C for 48 hours.”

According to the checklist, it is required to have a “Data sources/measurement” content to describe the sources of data and details of methods of assessment (measurement), and also to describe the comparability of assessment methods if there is more than one group. Therefore, these were found in our manuscript to fulfill the requirement as follow:

Sources of data
Patient data (Page 5 Line 14-18)
“Patients’ demographic information, history of hospitalization, underlying conditions, and the presence of indwelling devices, wounds or ulcers, were collected by patients’ review chart and from the hospital computer information system. Antimicrobial treatment history within three months prior to MRSA screening was also analyzed.”

Area of LTCFs (Page 7 Line 15-20)
“The overall MRSA prevalence in LTCFs was compared with the average living area (square feet per person) per resident of different LTCFs, where the size of each LTCF was estimated from the government registrations and commercial websites for property trading. Anonymous on-site assessment was made by two co-authors to validate the information. The official capacity and occupancy of each LTCF was collected from the community geriatric assessment team.”

Details of methods of assessment (Page 6 Line 9 - Page 8 Line 3)

“Acquisition of MRSA among residents during their stay in LTCFs and in hospitals
To obtain the number of MRSA carriers among the LTCF residents being hospitalized, MRSA screening from nasal swabs were taken within 24 hours after the first admission of the LTCFs subgroup in our acute hospital. Acquisition of MRSA in LTCFs was defined as a negative MRSA screening at LTCFs between 1 July and 31 August 2011 followed by a positive result upon hospital admission screening. The time interval between the first
negative sample collected at LTCFs and the positive hospital admission screening was recorded. Similarly, to investigate the nosocomial MRSA acquisition among LTCF residents during their hospital stay, nasal swabs for MRSA screening were repeated at the acute and 3 extended-care hospitals before being discharged to the patients’ respective LTCFs. Nosocomial acquisition of MRSA was defined as the conversion of nasal MRSA carriage status from negative to positive during hospitalization. The time interval between hospital admission and discharge was recorded.

In order to estimate the MRSA colonization pressure in different patient groups, the formula for calculating colonization pressures per 1000-LTCFs resident-days was used as described previously [23]. The colonization pressure for LTCF residents was defined as the ratio of MRSA-carrying LTCF resident-days over the total number of LTCF resident-days, while the colonization pressure for hospitalized LTCF residents was defined as the ratio of imported-MRSA hospitalized-days over the total number of hospitalized days during the study. The incidences of MRSA transmission during their stay in LTCFs and in hospitals were measured in terms of MRSA transmission per 1000-colonization-days. The data on the total number of LTCFs resident-days and hospitalized days were collected from the community geriatric assessment team and the hospital record office respectively.

**Relationship between MRSA prevalence and living area per LTCFs resident**

As the general demographic factors showed no significant difference on MRSA acquisition between the two subgroups, we sought to look for other LTCFs specific contributing factor. Hong Kong is a highly populated city with limited land resource, while LTCFs are of great demand and are often crowded. Thus, we postulate that living area may affect the living standard of the elderly and the average living area in LTCFs may correlate with the hygienic standard of the LTCFs in Hong Kong. The overall MRSA prevalence in LTCFs was compared with the average living area (square feet per person) per resident of different LTCFs, where the size of each LTCF was estimated from the government registrations and commercial websites for property trading. Anonymous on-site assessment was made by two co-authors to validate the information. The official capacity and occupancy of each LTCF was collected from the community geriatric assessment team. The living area per person was defined as the total area of the LTCF divided by the number of residents at the time of study.

**Microbiological analysis**

Swab specimens collected from study subjects were delivered to the laboratory immediately for inoculation on MRSA chromID culture media (bioMérieux), which was incubated aerobically at 35°C for 48 hours. MRSA colonies were confirmed as previously described [19]. DNA was extracted from S. aureus colonies using alkaline lysis method and spa typing was performed for the first isolate from each person as described previously [9,
10, 24]. Repeat sequences were analyzed according to the Ribosomal Differentiation of Micro-organisms (RIDOM) database on Staphylococcus aureus (http://www.ridom.de/staphtype) for spa typing.

According to the checklist, it is required to have a “Bias” to address the potential sources of bias. In the revised manuscript, we have included the potential sources of bias that this study is only limited to patients in the Hong Kong West:

(Page 4 Line 10-12)
“A prospective study was conducted from 1 July to 31 December 2011 to determine the prevalence and acquisition of MRSA among LTCFs and their network hospitals in the Hong Kong West Cluster, which served a population of 0.53 million.”

According to the checklist, it is required to have a “Study size” to explain how the study size was arrived at. Therefore, we have a paragraph in our revised manuscript to fulfill the requirement as follows:

(Page 4 Line 23 – Page 5 Line 3)
“In this study, we recruited all residents who agreed to join this study from the 57 LCTFs under the coverage of community geriatric assessment service in our healthcare region. Also, we included nasal MRSA screening results of patients admitted to the acute hospital within the study period between 1 July and 31 December 2011 into the study for analysis and data comparison.”

According to the checklist, it is required to have a “Quantitative variables” to explain how the quantitative variables were handled in the analyses. Therefore, we have mentioned these factors in our manuscript to fulfill the requirement:

**Quantitative variables**

Handling of MRSA colonization pressure in different patient group  
(Page 6 Line 22- Page 7 Line 7)
“In order to estimate the MRSA colonization pressure in different patient groups, the formula for calculating colonization pressures per 1000-LTCFs resident-days was used as described previously [23]. The colonization pressure for LTCF residents was defined as the ratio of MRSA-carrying LTCF resident-days over the total number of LTCF resident-days, while the colonization pressure for hospitalized LTCF residents was defined as the ratio of imported-MRSA hospitalized-days over the total number of
hospitalized days during the study. The incidences of MRSA transmission during their stay in LTCFs and in hospitals were measured in terms of MRSA transmission per 1000-colonization-days. The data on the total number of LTCFs resident-days and hospitalized days were collected from the community geriatric assessment team and the hospital record office respectively.”

Microbiological analysis (Page 8 Line 1-8)
“Swab specimens collected from study subjects were delivered to the laboratory immediately for inoculation on MRSA chromID culture media (bioMérieux), which was incubated aerobically at 35°C for 48 hours. MRSA colonies were confirmed as previously described [19]. DNA was extracted from S. aureus colonies using alkaline lysis method and spa typing was performed for the first isolate from each person as described previously [9, 10, 24]. Repeat sequences were analyzed according to the Ribosomal Differentiation of Micro-organisms (RIDOM) database on Staphylococcus aureus (http://www.ridom.de/staphtype) for spa typing.”

According to the checklist, it is required to have a “Statistical methods” to describe all statistical methods. Therefore, we have included the following paragraph in our manuscript to fulfill the requirement:

Statistical Analysis (Page 8 Line 11-17)
“For statistical calculation, the Chi-square test, Fisher’s exact test, t-test, or the Mann–Whitney U-test was used where appropriate. Pearson correlation was calculated to evaluate the potential linear relationship between overall MRSA prevalence in the LTCFs and the average living area (square feet per person) per LTCF resident. All reported p-values were two-sided. A p-value of <0.05 was considered statistically significant. Computation was performed using the Predictive Analytics Soft Ware (PASW) Version 18.0 (formerly SPSS) for Windows and R 2.14.0.”

Reviewer 1 comments – continues:

2. Writing that admission cultures were collected "immediately" doesn't mean anything. There are definitions that are commonly used that reference some maximum amount of time post admission (usu 24-72 hours), which are lacking here.

Answer:
In our logical sense, we assume “immediately” as <24 hours after ward admission. Since the reviewer requested for clear description on the time of swab collection, we amended the text by replacing “immediately” to “within 24 hours after first admission”
To obtain the number of MRSA carriers among the LTCF residents being hospitalized, MRSA screening from nasal swabs were taken within 24 hours after the first admission of the LTCFs subgroup in our acute hospital.

3. The article also continues to suffer from poor writing despite that the authors state that there was "copyediting process by a native English speaker." There are grammar mistakes in the first sentence of the introduction.

Answer:
In response to the comment, we have further revised our manuscript. The amended sentences and paragraphs have been rewritten as follow:

Abstract

“The relative contribution of long term care facilities (LTCFs) and hospitals in the transmission of methicillin-resistant Staphylococcus aureus (MRSA) is unknown.”

“In 40 LTCFs, 436 (21.6%) of 2020 residents were identified 'MRSA-positive'. The incidence of MRSA transmission per 1000-colonization-days among the residents during their stay in LTCFs and hospitals was 309 and 113 respectively, while the colonization pressure in LTCFs and hospitals was 210 and 185 per 1000-patient-days respectively.”

“MRSA spa type t1081 was the most commonly isolated lineage in both LTCF residents (76/121, 82.8%) and hospitalized patients (51/87, 58.6%), while type t4677 was significantly associated with LTCF residents (24/121, 19.8%) compared with hospitalized patients (3/87, 3.4%) (p<0.001)”

“Also, an inverse linear relationship between MRSA prevalence in LTCFs and the average living area per LTCF resident was observed (Pearson correlation -0.443, p=0.004), with the odds of patients having MRSA decreased by 0.90 times with each 10 square feet increase in living area.”
“MRSA transmission was elucidated to be more serious in LTCFs than in hospitals.”

**Introduction**

(Page 3 Line 2-9)

“Methicillin-resistant Staphylococcus aureus (MRSA) has emerged worldwide as an important nosocomial pathogen since 1980s [1]. The transfer of colonized or infected patients between hospitals and repeated hospital admission were identified to be the major causes of nosocomial MRSA acquisition [2, 3]. The risk factors for hospital-acquired MRSA were antibiotic exposure, length of stay, admission to intensive care unit (ICU), colonization pressure, and underlying co-morbidities. Hence, implementation of antimicrobial stewardship program, hand hygiene campaign, and the use of a bundle approach in the adult ICU were highly recommended for the effective control of nosocomial MRSA transmission [4-7]."

(Page 3 Line 10-11)

“In Hong Kong, the increasing number of elderly persons urged the needs for long term institutional care and frequent hospitalization.”

(Page 3 Line 15-19)

“Other studies focusing on the prevalence and risk factors for MRSA colonization have also observed that a recent history of hospitalization is an important determinant for MRSA colonization among the population in LTCFs [8, 11-18]. However, the relative contribution of LTCFs and hospitals to the degree of MRSA transmission within the healthcare setting is undetermined.”

(Page 3 Line 20-21)

“In this study, we analyzed the acquisition of MRSA in LTCFs and hospitals in our locality.”

**Methods**

(Page 4 Line 12-14)

“LTCFs is a collective term for all long term nursing facilities that provide daily nursing care for their residents including the use of feeding tubes, urinary catheters and other medical devices.”

(Page 4 Line 17-23)
“Patients from LTCFs within our healthcare region would be admitted to the acute hospital for management. Once stabilized, patients would either be discharged to their original LTCFs or transferred to one of the 3 extended-care hospitals within the regional hospital network before returning to the LTCFs. Community geriatric assessment team, comprising of geriatricians, nurses and allied health professionals, would provide regular on-site visits to the LTCFs within our healthcare region for comprehensive medical follow-up and recommendations on infection control measures.”

(Page 5 Line 9-10)

“The objectives of the study and procedures involved were explained to the community geriatric assessment team and LTCFs representatives in our healthcare region.”

(Page 5 Line 13-15)

“They were trained by infection control nurses on the techniques in taking nasal swabs according to a standard protocol as previously described [19].”

(Page 5 Line 20- Page 6 Line 4)

“To determine the differences between patients with probable LTCF-acquired MRSA and probable hospital-acquired MRSA, patients were classified into “LTCF subgroup” and “hospital subgroup” for further analysis. LTCF residents who had no history of hospitalization in the past 12 months are classified as ‘LTCFs subgroup’, while “hospital subgroup” consisted of non-LTCF patients who were admitted to the acute hospital within the study period. An exposure window of 12 months was selected as the length of monitoring period, since the median carriage of MRSA was found to be 8.5 months after hospital discharge [20] and the 12-months period has also been adopted in other MRSA transmission epidemiology studies [21, 22].”

(Page 6 Line 5-7)

“The risk factors for MRSA acquisition in the LTCFs subgroup were analyzed, and the MRSA Staphylococcus protein A (spa) type distribution between LTCFs and hospital subgroups were also compared.”

(Page 6 Line 10-14)

“To obtain the number of MRSA carriers among the LTCF residents being hospitalized, MRSA screening from nasal swabs were taken within 24 hours after the first admission of the LTCFs subgroup in our acute hospital. Acquisition of MRSA in LTCFs was defined as a negative MRSA screening at LTCFs between 1 July and 31 August 2011 followed by a positive result upon hospital admission screening.”
“Similarly, to investigate the nosocomial MRSA acquisition among LTCF residents during their hospital stay, nasal swabs for MRSA screening were repeated at the acute and 3 extended-care hospitals before being discharged to the patients’ respective LTCFs.”

“In order to estimate the MRSA colonization pressure in different patient groups, the formula for calculating colonization pressures per 1000-LTCFs resident-days was used as described previously [23].”

“As the general demographic factors showed no significant difference on MRSA acquisition between the two subgroups, we sought to look for other LTCFs specific contributing factor. Hong Kong is a highly populated city with limited land resource, while LTCFs are of great demand and are often crowded. Thus, we postulate that living area may affect the living standard of the elderly and the average living area in LTCFs may correlate with the hygienic standard of the LTCFs in Hong Kong. The overall MRSA prevalence in LTCFs was compared with the average living area (square feet per person) per resident of different LTCFs, where the size of each LTCF was estimated from the government registrations and commercial websites for property trading. The official capacity and occupancy of each LTCF was collected from the community geriatric assessment team.”

“Swab specimens collected from study subjects were delivered to the laboratory immediately for inoculation on MRSA chromID culture media (bioMérieux), which was incubated aerobically at 35°C for 48 hours.”

“For statistical calculation, the Chi-square test, Fisher’s exact test, t-test, or the Mann–Whitney U-test was used where appropriate. Pearson correlation was calculated to evaluate the potential linear relationship between overall MRSA prevalence in the LTCFs and the average living area (square feet per person) per LTCF resident.”

“Results
"Of the 57 LTCFs under the coverage of community geriatric assessment service at our healthcare region, 40 (70.0%) LTCFs participated in our study.”
"Nursing care was provided by on-site staff but the medical problems were taking care of by the community geriatric assessment team who visits at regular basis. Thirteen percent of residents have in situ feeding tubes, urinary catheters or other medical devices requiring special care. During the study period, 2900 residents lived in these LTCFs, of which 2020 residents (70.0%) consented for the study. Among the 2020 recruited residents, 436 of them (21.6%) were identified to be MRSA positive (Figure 1) through the LTCFs on-site surveillance screening. Compared with the other 1584 recruited residents without MRSA colonization, MRSA carriers had significantly more episodes of hospitalization (72.2% vs 53.7%, p<0.001) and longer cumulative length of hospital stay in the past 12 months (Supplementary Table 1)."

"During the concurrent period, admission MRSA screening performed for all subjects in the study cohort within 24 hour of admission to the acute hospital. Among the patients from 1290 consecutive hospital admissions, 204 (15.8%) were identified as MRSA-positive (Figure 1). A significantly higher proportion of MRSA-positive patients were admitted directly from the LTCFs (57.4%) comparing to non-LTCF residents (13.6%) [p<0.001; odd ratio of 8.52 (6.15-11.82)] (supplementary Table 2)."

"Eight hundred and fifty-four (42.3%) of 2020 LTCF residents with no history of hospitalization in the past 12 months (LTCFs subgroup) and 1025 (79.5%) of 1290 non-LTCF hospitalized patients (hospital subgroup) were selected for further analysis to determine the differences between patients with probable LTCF-acquired MRSA and probable nosocomial-acquired MRSA."

"The risk factors for MRSA colonization in the LTCFs and hospital subgroups as determined by logistic regression analysis are shown in Table 1. Residing in LTCFs was shown to be a significant risk factor for MRSA colonization. Moreover, the presence of urinary catheter, chronic cerebral conditions, the use of β-lactam / β-lactamase inhibitors within three months of MRSA screening were also found to be significant risk factors. After adjusting the confounding factors, the estimated odds for persons having MRSA in LTCFs were 3.4 times higher than those not residing in LTCFs."
"Among the 1584 LTCF residents who were found to be non-MRSA carriers during the on-site surveillance period between 1 July and 31 August 2011, 337 of them (21.3%) were subsequently admitted to the acute hospitals, and were subjected to MRSA admission and discharge screening (Figure 1). Admission screening had identified 65/337 (19.3%) residents to have become MRSA-positive suggesting that they had acquired MRSA in LTCFs after on-site surveillance. The median time of MRSA detection from surveillance to admission was 77 days (range, 9-181 days). Given that the 436 MRSA-positive residents identified during the on-site surveillance had stayed in the 40 LTCFs for 66,802 days, and the overall 2020 residents had stayed in the LTCFs for 317,752 days during our study period, the colonization pressure of MRSA in LTCFs would be 210 per 1000-resident-days [(MRSA resident-days of 436 MRSA-positive residents was 66802 days) / (total resident-days of 2020 residents was 317752 days) x 1000 days]. With the use of these information, the rate of MRSA transmission of the 65 defined LTCFs acquired MRSA was estimated to be 309 MRSA transmissions per 1000-colonization-days among LTCF residents [(65 residents acquired MRSA in LTCFs) / (colonization pressure of 210 per 1000-resident-days) x 1000 days]."

(During hospitalization, 21 (7.7%) out of 272 the MRSA-negative LTCF residents acquired MRSA. The median time of MRSA detection was 7 days (ranged 1-31 days). Given that the 65 LTCF-acquired MRSA residents stayed in hospital for a total of 396 days, and the 337 non-MRSA carrying LTCF residents, during the on-site surveillance, stayed for 2137 days during our study period, the MRSA colonization pressure for hospitalized LTCF residents was 185 per 1000-patient-days [(imported-MRSA patient-days of 396 days) / (total patient-days of 337 residents of 2137 days) x 1000 days]. Based on this data, we further estimated the rate of MRSA transmission for hospitalized LTCF residents to be 113 MRSA transmissions per 1000-colonization-days [(21 residents acquired MRSA in hospital) / (colonization pressure of 185 per 1000-patient-days) x 1000 days]. The demographic characteristics of persons with MRSA acquisition in LTCFs and hospitals were not significantly difference (Table 2)."

"An inverse linear relationship between MRSA prevalence in LTCFs and average living area (square feet per person) per LTCF resident was found (Figure 3). Pearson correlation of MRSA prevalence per LTCF and living area per resident was \(-0.443\) (p=0.004)."

"This diversity in spa type was also observed among the 337 patients who were MRSA-negative during LTCFs on-site surveillance who were subsequently hospitalized within the study period. The 65 patients (65/337,
19.3%) who were identified to be positive with MRSA at the admission screening had spa types which belonged to the LTCFs subgroup, while the 272 (272/337, 80.7%) who were MRSA-negative at admission screening but later became MRSA-positive at discharge screening had spa types which belonged to the hospital subgroup.

**Discussion**

(Page 13 Line 4-14)

“This finding is comparable to those in the US [25] study but higher than other studies conducted in Germany [11, 18], Belgium [12, 16], and Spain [15]. Similar to the previous studies, history of hospitalization, chronic comorbidity, indwelling devices, wound or ulcer, and antimicrobial therapy were found to be risk factors for MRSA colonization in our study [11, 12, 15, 16, 18]. Moreover, residence in LTCFs and a long cumulative length of hospital stay in the past 12 months were again found to be significant risk factors for MRSA colonization by univariate analysis in our concurrent admission screening [26-30]. Transfer of patients between LTCFs and hospitals create a vicious cycle which perpetuated MRSA transmission. Hence, it is of great importance to investigate the relative contribution of LTCFs and hospitals in the transmission dynamics of MRSA in the healthcare setting.”

(Page 13 Line 17-19)

“The incidence of MRSA transmission per 1000-colonization-days among LTCF residents was also three times higher than that of the hospitalized LTCF residents, given that the colonization pressure in both LTCFs and hospital were similar.”

(Page 13 Line 20- Page 14 Line 7)

“While there was no difference in risk factors between patients with LTCFs-acquired and nosocomial-acquired MRSA, it was noted that the average living area per resident in different LTCFs was an important surrogate marker reflecting the hygienic standard of LTCFs. An inverse linear relationship between MRSA prevalence in the LTCFs and the average living area per resident was found. Provided that the other risk factors were held constant, the odds of patients acquiring MRSA is reduced by 0.9 times with each increment of 10 square feet in living area. To our best knowledge, our study is the first quantitative analysis to demonstrate that living area per person could be a determinant of MRSA prevalence in LTCFs. This finding is particularly relevant for urban cities with a high population density like Hong Kong with an average land price of USD 1000 per square feet. The supply of residential land is limited and living environments are characterized by extremely compact multi-storey apartments [31].”

(Page 14 Line 10-11)
“Therefore, this appears to be a suitable surrogate marker of LTCFs in terms of the overall standard of care, hygiene and infection control.”

(Page 14 Line 16-18)

“Type t002 was commonly found in hospitalized patients in our region and the United States [10, 34, 35] whereas type t4677 had not been reported in the community or hospital setting previously.”

(Page 15 Line 3-4)

“There are several limitations in our study. Firstly, only 70% of the LTCF residents consented for this study introducing potential bias in subject selection.”

(Page 15 Line 5-8)

“Furthermore, the sensitivity of detection [37] may be compromised in subjects with low microbial load while not on antibiotic therapy [19, 38]. Chromogenic agar, however, was used to improve sensitivity and cost-effectiveness [39].”

(Page 15 Line 9-14)

“As most of the LTCFs have satisfied the minimal requirement of the government, living area per resident was chosen as an important surrogate marker reflecting the hygienic standard of LTCFs. We did not screen for MRSA carriage among healthcare workers in the LTCFs and hospitals since the benefit of carriage eradication is not established in non-outbreak setting [41], despite a recent study suggesting that both residents and staff were involved in MRSA transmissions [42].”

(Page 15 Line 16-19)

“More resources should be allocated to improve the infection control measure of LTCFs and further studies are necessary to understand key factors, such as space availability, that lead to high level of MRSA transmission within LTCFs.”

Tables

(Table 1 Note)

“Note. After adjusting the other confounding factors, the estimated odds for persons having MRSA in LTCFs is exp (1.218) ≈ 3.4 times than those not residing in LTCFs.”
Also, we have added a new figure (Figure 2 in revised submission) to replace the original Figure 2. The new Figure 2 is an overview of the follow-up logistics for handling both LTCF residents and hospitalized patients recruited in this study.

The original Figure 2 is renamed as Figure 3 in the revised submission.

We hope that the revised manuscript is acceptable after our extensive revision mentioned above.

**Editor’s comments:**

As you can see the reviewers were very split in their advice and as a result we discussed this further with our editorial board. Whilst they thought your manuscript contained useful data they shared the concerns of Reviewer 1 that at present this was organized and presented in a sub-optimal way.

1. Two specific examples were the fact that the opening line of the discussion "regarding increase in prevalence over the past 6 years" is the first mention of this fact.

   **Answer:**
   We appreciate the editor's comment. We have described the prevalence of MRSA in recent 6 years in the “Introduction” paragraph Page 3 Line 14-15 with reference No. 8 and 9 as supporting articles. Then we described the prevalence of MRSA in LCTFs in this study in the “Results” and “Figure 1”. I think the misunderstanding is due to the unclear description in the discussion paragraph.

   In responding to the editor’s comment, we added the description of the prevalence of MRSA in LTCFs and reference no. 8 and 9 in the discussion paragraph as follow:

   (Page 13 Line 2-4)

   “Our study showed that the prevalence of MRSA among LTCFs in Hong Kong had increased substantially from 3-5% to over 20% (436 MRSA positive /2020 residents in 40 LTCFs) (Figure 1) in the recent six years [8, 9].”

2. and that it is not specified exactly when swabs were taken (i.e. is immediately within 2 hours of admission?).

   **Answer:**
We appreciate the editor’s comment. This is the same to Review 1 Question 2. In responding to the editor’s comment, we have amended the text by replacing “immediately” to “within 24 hours” as follow:

(Page 6 Line 11-13)

“To obtain the number of MRSA carriers among the LTCF residents being hospitalized, MRSA screening from nasal swabs were taken within 24 hours after the first admission of the LTCFs subgroup in our acute hospital.”

3. In addition it was felt that more descriptive titles for the tables and figures would benefit readers.

Answer:
We appreciate the editor’s comment. For Table 1, Table 4, and Figure 1, and new Figure 2 (new in revised submission), descriptions in titles had been amended as follow:

Table 1.
Logistic regression analysis for the estimated probability of detection of MRSA with the following risk factors in the combined LTCFs subgroup and hospital subgroup

Table 4.
Logistic regression analysis for the estimated probability of detection of MRSA with the following risk factors in the LTCFs subgroup

Figure 1.
Overview of the MRSA colonization among LTCF residents and hospitalized LTCF residents in the healthcare region, Hong Kong West

Figure 2. (New in Revised submission)
Overview of the logistic of follow up analysis in both LTCF residents and hospitalized patients recruited in our study.