MRSA transmission dynamics among interconnected acute, intermediate- and long-term healthcare facilities in Singapore

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40-word Summary:

MRSA transmission dynamics among interconnected acute, and intermediate and long-term care facilities (ILTCs) varied between clones. Clonal complexes ST22 and ST45 successfully spread throughout the healthcare system, and are established in ILTCs. MRSA prevention is critical in ILTCs.

Abstract (250 words)

Background

Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most common healthcare-associated multidrug-resistant organism. Despite the interconnectedness between acute hospitals (AHs) and intermediate- and long-term care facilities (ILTCs), the transmission dynamics of MRSA between healthcare settings is not well understood.

Methods

We conducted a cross-sectional study in a network comprising an AH and five closely-affiliated ILTCs in Singapore. A total of 1,700 inpatients were screened for MRSA over a 6-week period in 2014. MRSA isolates underwent whole genome sequencing, with a pairwise SNP (Hamming distance) cutoff of 60 core genome SNPs used to define recent transmission clusters (clades) for the three major clones.

Results

MRSA prevalence in intermediate-care (ITCs) (29.9%) and long-term care facilities (LTCs) (20.4%) were significantly higher than in the AH (11.8%) ($p<0.001$). The predominant clones were ST22 (183, 47.8%), ST45 (129, 33.7%) and ST239 (26, 6.8%), with greater diversity of STs in ILTCs relative to the AH. A large proportion of the clades in ST22 (14/21, 67%) and ST45 (7/13, 54%) included inpatients from the AH and ILTCs. The most frequent source location of the inter-facility transmissions was the AH (*n*=28, 36.4%).

Conclusions

MRSA transmission dynamics between the AH and ILTCs were complex. The greater diversity of STs in ILTCs suggests that the eco-system in such settings might be more conducive for intra-facility transmission. ST22 and ST45 have successfully established themselves in ILTCs. The importance of interconnected infection prevention and control measures and strategies cannot be overemphasized.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most common healthcare-associated drug-resistant organisms globally, especially in Asia [1]. MRSA has also evolved from being an almost purely healthcare-associated pathogen to one that is increasingly isolated from the community and from livestock, such that the traditional classifications of healthcare-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA) are progressively blurred [2]. There remain relatively few successful HA-MRSA clones that have spread globally. In Asia, the major successful HA-MRSA clones belong to multilocus sequence type (ST) 239, ST5 (New York-Japan clone), ST22 (UK-EMRSA-15) [1,3], and lately ST45 [4-6].

HA-MRSA emerged in Singapore in the late 1970s [7]. Between the late 1980s and 2000, virtually all HA-MRSA were ST239 [3,7]. This changed with the importation of ST22 MRSA around 2000, which became the dominant HA-MRSA clone by 2010 [3,7-9]. Phylogenetic analysis of representative isolates of both HA-MRSA clones across three major acute care hospitals (AHs) in Singapore revealed interdependent evolution for both clones, suggesting that frequent exchanges of patients and staff had occurred between the hospitals[3]. Since 2010, a third global clone of HA-MRSA,ST45, has appeared in Singaporean hospitals and is increasing in prevalence [5].

Besides horizontal transfers between AHs, vertical transfers of patients from AHs to intermediate- and long-term care facilities (ILTCs) are common in Singapore. Several studies suggesting that ILTCs – with their reduced staff-to-patient ratios and less stringent infection prevention practices – may serve as reservoirs of MRSA within the

healthcare system [10-12].

Whole genome sequencing (WGS) is fast emerging as the new gold standard for bacterial molecular epidemiology [13-18]. Various studies looking at within-host single nucleotide polymorphism (SNP) diversity and MRSA transmission have defined the cut-off for a recent (i.e. days and weeks rather than months) transmission event as 40 to 60 pairwise core genome SNPs (Hamming distance) [16-18]. In examining the spread of ST239 within and between intensive care units of a hospital in northeastern Thailand, a (Hamming) pairwise distance cutoff of 60 SNPs was used to define recent transmission clusters (clades) which were epidemiologically supported. We therefore sought to investigate the MRSA transmission dynamics between an AH and its closely affiliated ILTCs using WGS, defining clades for further analysis via Hamming distance calculations.

METHODS

Study design and settings

A cross-sectional study was conducted in a 1,700-bed adult tertiary-care AH in Singapore and its five most closely-affiliated ILTCs: a 105-bed rehabilitation center (ITC 1), a 78-bed community hospital (ITC 2), a 235-bed community hospital (ITC 3), a 234-bed nursing home (LTC 1), and a 164-bed chronic sick unit (LTC 2). The study took place over a six-week period from June 2 to July 9 2014. We randomly selected 999 inpatients with >48 hours stay in the AH to participate in the study. All residents of the ILTCs were included.

Bacterial isolates

Nasal, axillary, and groin swabs were obtained from all study subjects sequentially over the six-week period in order to capture the contemporaneity of MRSA isolates from the various healthcare facilities, as the estimated mutation rate of one core single-nucleotide polymorphism (SNP) for MRSA is approximately every six weeks [3,15]. MRSA was cultured from the swabs, and DNA extracted from the isolates, using conventional methods (see Supplementary Methods for more details).

Whole genome sequencing and data access

WGS was performed following previously described protocols (Supplementary Methods) [3,15]. Short reads for all sequenced isolates have been submitted to the European Nucleotide Archive (ENA; http://www.ebi.ac.uk/ena/) under study accession number PRJEB9390. Individual accession numbers of sequences and assemblies for all isolates are listed in Supplementary Table 1.

Data analysis

Quantitative analysis

The differences in MRSA prevalence between healthcare facilities were compared using the Chi-square test, with the odds ratios and 95% confidence intervals (CI) of the associations estimated. Differences in age and duration of stay were compared using the Student's t-test and Wilcoxon rank-sum test respectively. All statistical analyses were performed using Stata version 13 (Stata Corp., College Station, TX).

Bioinformatics and phylogenetic analysis

The sequence reads were aligned against the appropriate reference sequences using SMALT (http://www.sanger.ac.uk/science/tools/smalt-0) and SNPs were identified as described previously (Supplementary Methods) [3]. Phylogenetic trees for major clones were constructed using RAxML v7.0.4 [19].

Determination of clades and parsimonious reconstruction of transmissions events

Single isolates were picked as representative of a sample site, and in some individuals there were multiple isolates from different sites. Where isolates were from the same ST, a primary isolate, representative of that individual, was chosen; sites were preferentially picked in the following sequence: nasal, groin, followed by axilla. Isolates belonging to different STs from the same individual were included in the analysis.

Hamming distances were calculated (Supplementary Figure 1). This cut-off was then used to define clades for each major ST. For each of the clades, parsimonious reconstruction of transmissions events between the different healthcare locations was conducted using the phylogenetic trees and associated healthcare setting metadata. The basal isolate in each clade was assigned as the origin state, and transmissions parsimoniously reconstructed onto the phylogeny from root to tips to identify inter- and intra-facility transmission events.

Ethics

Ethical approval for the study was obtained from the Domain Specific Research Board, National Healthcare Group.

RESULTS

There were 1,700 subjects screened for MRSA during the study period, with a participation rate of 86% at the ILTCs. Subjects across the healthcare facilities were similar in terms of age and gender, whereas subjects in LTCs had longer duration of stay compared to subjects in ITCs and the AH (Table 1). The prevalence of MRSA in ITCs (29.9%) and LTCs (20.4%) were significantly higher than in the AH (11.8%) (p<0.001).

We sequenced 383 MRSA isolates from 289 subjects from the prospective screening. The predominant lineages were ST22 (n=183, 47.8%), ST45 (n=129, 33.7%), ST239 (n=26, 6.8%), and ST1 (n=18, 4.7%), with small numbers of STs from other clonal complexes (CCs) (n=27, 7.0%). ST22 was more prevalent in the AH (53%) and ITCs (53%) than in the LTCs (31%) (P= 0.005) (Figures 1A-C). In contrast, LTCs had the greatest diversity of MRSA clones (Figure 1C). CA-MRSA clones (ST59 and ST30) were observed in an intermediate-care (ST59, n=2, 0.5%) and a long-term care facility (ST30, n=2, 0.5%) respectively. Seventy-eight subjects (27.0%) had MRSA recovered simultaneously from different body sites, of which 65 (83.3%) had isolates with the same ST, whereas the remainder had isolates belonging to two different STs at different sites.

Three major HA-MRSA lineages were the focus of MRSA transmission dynamic investigations: ST22, ST45 and ST239. In total 270 isolates were subject to phylogenetic analysis to elucidate the fine-scale genetic relationships between representative isolates from the subjects in each ST (Figure 2). The ST22 isolates (n=143) were differentiated by 2775 SNP sites, the ST45 (n=107) by 1533 SNP sites, and ST239 (n=20) by 637 SNP sites.

The healthcare origins of the isolates in relation to phylogenetic relationships were categorized as heterogeneous, with isolates from all six settings distributed throughout the phylogenies (Figure 2). This is consistent with the interconnectivity of the healthcare network. The narrow temporal sampling of this study enabled us to look for evidence of both intra- and inter-facility transmission of MRSA. Isolates that are part of a transmission chain will share a recent common ancestor, and therefore will be phylogenetically linked and genetically similar. In the phylogenies of the three main MRSA populations, there were clusters of isolates from the same healthcare setting suggestive of intra-facility transmission. In addition, there were clusters composed of isolates of mixed origins indicating that inter-facility transmission has occurred.

The majority of the subjects had isolates that were found in Hamming defined clades (Figure 2). In the ST22 population, 21 clades were identified comprising 124 isolates (86.7%) (Figure 2A), consistent with the distinct clusters observed on the tree. Similarly in the ST45 population, 13 clades comprising 95 isolates (88.8%) (Figure 2B) were identified. In the ST239 population this identified six clades comprising 19/20 isolates (95.0%) (Figure 2C).

Among the clades, 30 (77%) had at least one patient from the AH. The remaining clades comprised of either ITCs alone (*n*=4), ITCs and LTCs (*n*=2), or LTCs alone (*n*=3). Except for two clades (clade 45_6 and clade 22_12, Supplementary Table 1), at least one subject in each clade had been hospitalized in the study AH or another AH within the preceding 12 months. The other subjects in almost all clades (except clusters 22_15 and

45_3, Supplementary Table 1) who had not had an acute hospitalization episode had shared the same ward with at least one subject with a recent AH hospitalization.

The largest clade was identified in the ST45 population (Cluster 45_12, 40 subjects; Supplementary Table 1), comprising predominantly of patients from the AH, whereas the second largest clade was from the ST22 (clade 22_2, 37 subjects; Supplementary Table 1) which had the majority of patients from ITCs.

A larger proportion of the clades in ST22 (14/21, 67%) compared to ST45 (7/13, 54%) included patients and residents from both the AH and ILTCs. The remaining clades comprised either of patients from the AH or residents from ILTCs. In contrast, 40% (2/5) of the clusters in the ST239 phylogeny comprised of patients from the AH only.

Transmission events within the clades were reconstructed parsimoniously using phylogenetic analyses. In total 193 transition events could be designated (Supplementary Table 2). Over half of the events (*n*=116, 60.1%) were identified as being intra-facility transmissions, with the AH having the largest number (*n*=59) of events, followed by ITC1 (*n*=18), ITC3 (*n*=17), LTC1 (*n*=11), ITC2 (*n*=6) and then LTC2 (*n*=5). Examining the inter-facility transmissions, the most frequent source location of the transmissions was the AH (*n*=28, 36.4%), followed by ITC3 (*n*=21, 27.3%), LTC2 (*n*=12, 15.6%), ITC2, (*n*=9, 1.7%), LTC1 (*n*=4, 5.2%) and then ITC1 (*n*=3, 3.9%). A summary of the transmissions identified in the clades is presented in Figure 3 and illustrates the pathways of transmissions.

DISCUSSION

This study provided insights into the population dynamics of MRSA within an interconnected healthcare network of an AH with its closely affiliated ILTCs. MRSA prevalence in AH (11.8%) was significantly lowest compared to intermediate-care (ITCs) (29.9%) and long-term care facilities (LTCs) (20.4%) ($p<0.001$). The predominant clones were ST22 (183, 47.8%), ST45 (129, 33.7%) and ST239 (26, 6.8%), with greater diversity of STs in ILTCs relative to the AH. A large proportion of the clades in ST22 (14/21, 67%) and ST45 (7/13, 54%) consists of inpatients from both the AH and ILTCs. AH was the major source location of inter-facility transmissions (n=28, 36.4%).

The transmission of MRSA within the network is a complex one. Contemporaneously, different MRSA clones were identified within the same healthcare institution and the same MRSA clade observed across healthcare settings. The higher MRSA prevalence observed in ILTCs relative to the AH in our study was consistent with other studies [10-12], and – combined with the finding of a greater diversity of STs in ILTCs – indirectly suggests that infection prevention practices are less stringent in the ILTCs. The observation that the predominant clonal lineages were ST22, ST45 and ST239 also reflects what was previously reported [5], with the major change being that of the increased prevalence of ST45 vis-à-vis ST239.

The Hamming distance defined clusters allowed us to examine the recent dynamics of the MRSA. Our results suggest that the current dominant lineage ST22 appeared to have successfully transmitted from acute hospitals to ILTCs. In the ST22 phylogenetic tree, isolates from ILTCs interspersed with isolates from the AH within many clades. Furthermore, almost 1 in 5 clades in ST22 included only patients/residents

from ILTCs, suggesting that ST22 was being spread independently within ILTCs. The same findings were made for ST45, with a suggestion that isolates from this ST might preferentially spread within ILTCs given that 40% of the clades comprised of isolates obtained only from ILTC subjects. Despite ST239 being the oldest HA-MRSA clone in Singapore, it did not appear to have transmitted as successfully as ST22 and ST45 across healthcare settings. It is unclear if this was the result of ST239 being outcompeted at the ILTCs by the other two STs, or if differential infection control practices at the various healthcare facilities had played a role in the divergent distribution of the STs.

Parsimonious reconstruction of transmission events suggests that the AH was the source of MRSA with regards to transmission between the AH and the ITCs; however, it was the reservoir with regards to the transmission from LTCs. This` result seems incongruent with the higher prevalence of MRSA in ILTCs but may be explained by the general flow of patient movements. AH inpatients tend to be transferred to ITCs and are then discharged home, with only a small percentage requiring transfer back to the AH. LTCs on the other hand are the terminal care facility for patients transferred there, who stay until they are deceased or develop an acute event requiring transfer back to the AH. Moreover, far fewer patients are transferred directly from AH to LTC as compared to AH to ITC, or ITC to LTC.

Our study was limited by the cross-sectional design and short sampling frame, and the results based on genomic analysis will need validation via a longitudinal study. Second, the overall movement of patients and staff between the healthcare facilities was not evaluated, factors which may inform resolution to the net transmission of

MRSA between the various healthcare facilities. A higher participation rate at both the AH and ILTCs would have made for a more rigorous study; however, the results are unlikely to change significantly given the participation rate of 86%.

In conclusion, we found that the transmission dynamics of MRSA between an AH and its closely affiliated ILTCs varied between MRSA CCs. ST22 and ST45 have not only receded ST239 in acute hospitals [3,5], but have also successfully established themselves in the ILTCs. The greater diversity of STs in ILTCs suggests that the eco-system in such settings might be more conducive for intra-facility transmission. Interconnected infection prevention and control measures and strategies, including sharing of information on MRSA-colonizers and best practices, should be instituted across acute hospitals and ILTCs in healthcare networks.

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Scottish Healthcare Associated Infection Prevention Institute consortium funding (CSO Reference: SIRN10).

Figures

Figure 1.

Distribution of methicillin-resistant *Staphylococcus aureus* (MRSA) clones in the A) acute hospital (AH), B) intermediate-care (ITC), and C) long-term care (LTC) facilities, by total number of isolates (*n*=383)

Figure 2.

Population structures of the dominant methicillin-resistant *Staphylococcus aureus* (MRSA) clones circulating in health care facilities defined as maximum likelihood phylogenetic trees based on core genome SNPs of: A) ST22 B) ST45; and C) ST239. Also shown (right-hand panels) are: clades of isolates defined by the pairwise 60 SNP cutoff (clusters are alternatingly colored from top to bottom, blue and red) and healthcare facilities. The trees are rooted with the reference used for mapping for each ST. In the case of CA-347, the ST45 reference, the branch has been collapsed. Tree branches colored blue link isolates that belong to a clade (as indicated in the right-hand panel). One ST22 isolate, CD141496, single locus variant of ST22, was excluded from the phylogenetic analysis due to its genetic distance from the rest of the isolates in the collection.

Figure 3

Schematic representation of the transmission dynamics of methicillin-resistant *Staphylococcus aureus* (MRSA) in the healthcare settings. For each of the clusters,

parsimonious reconstruction of transmissions events between the different healthcare facilities were conducted using the phylogenetic trees and healthcare setting metadata. The origin of the basal isolate in each cluster was assigned as the initial state, and subsequent transmissions parsimoniously reconstructed to identify inter- and intra-facility transmission events. The arrows are scaled in size according to the number of observed inter-facility transmission events, and the circles representing the 6 different healthcare locations are scaled in size according to the number of intra-facility transmission events identified.

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FIGURES

Figure 1-A.

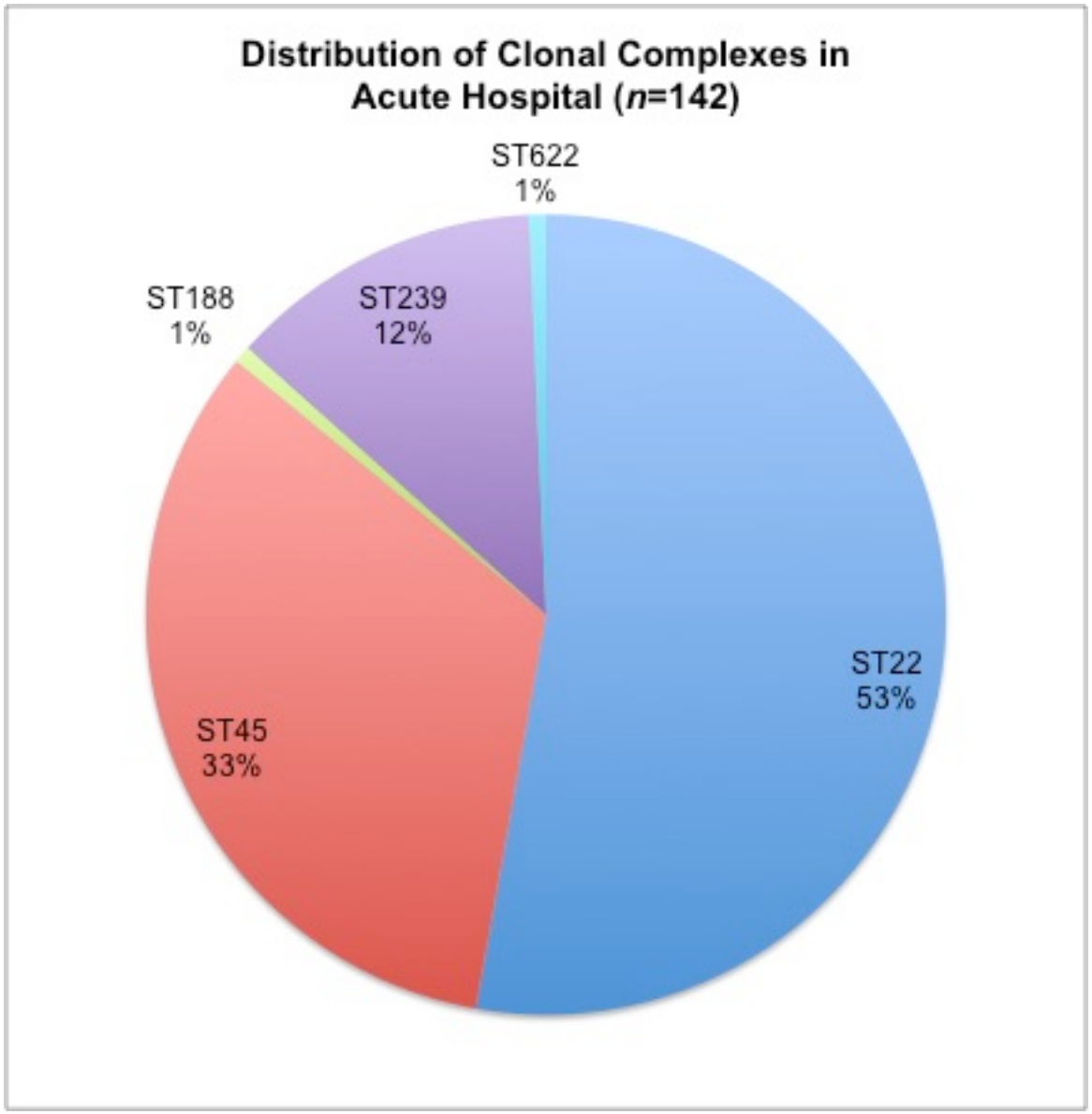


Figure 1-B. Distribution of Clonal Complexes in Intermediate Care Facilities (*n*=118)

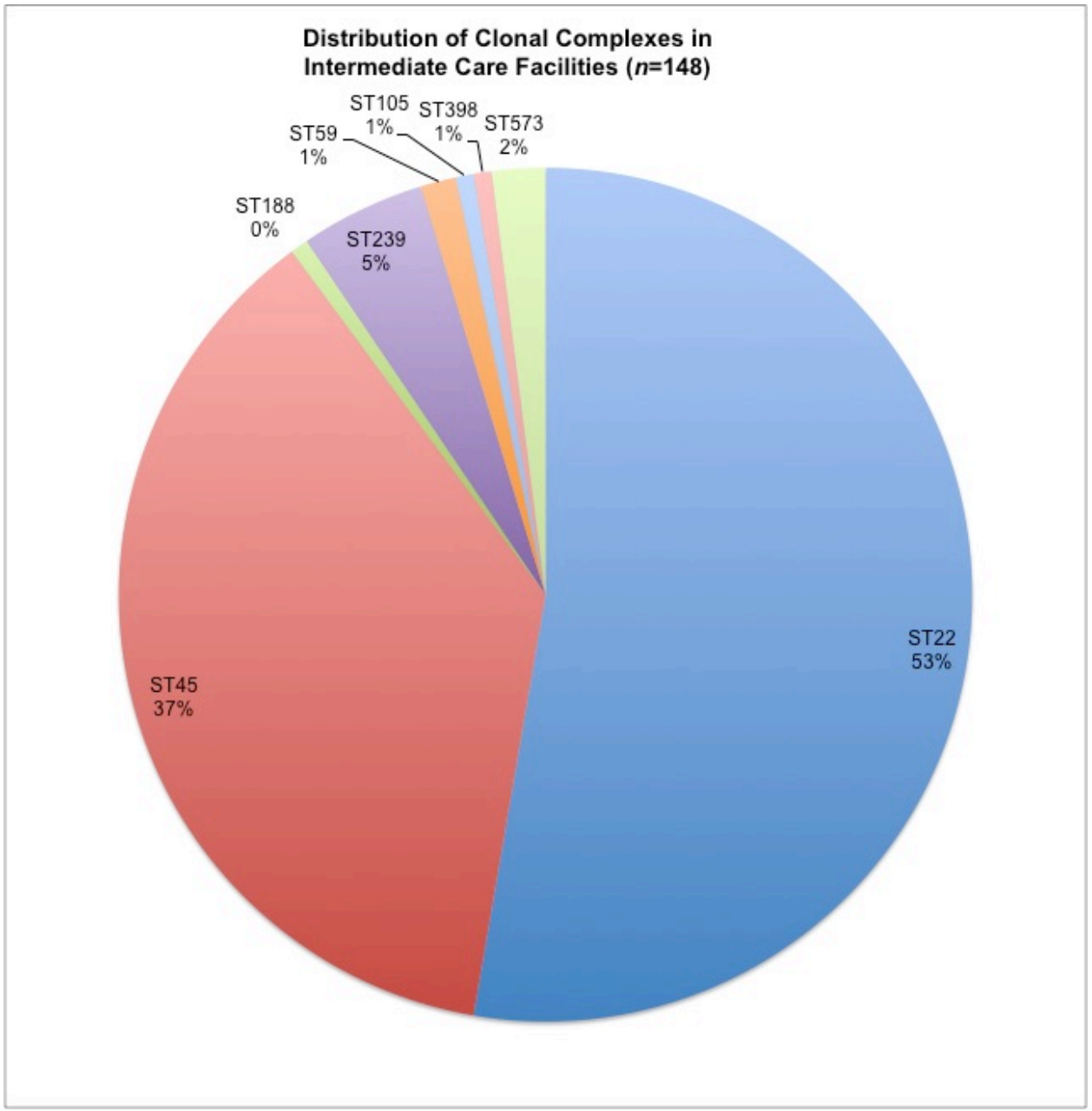
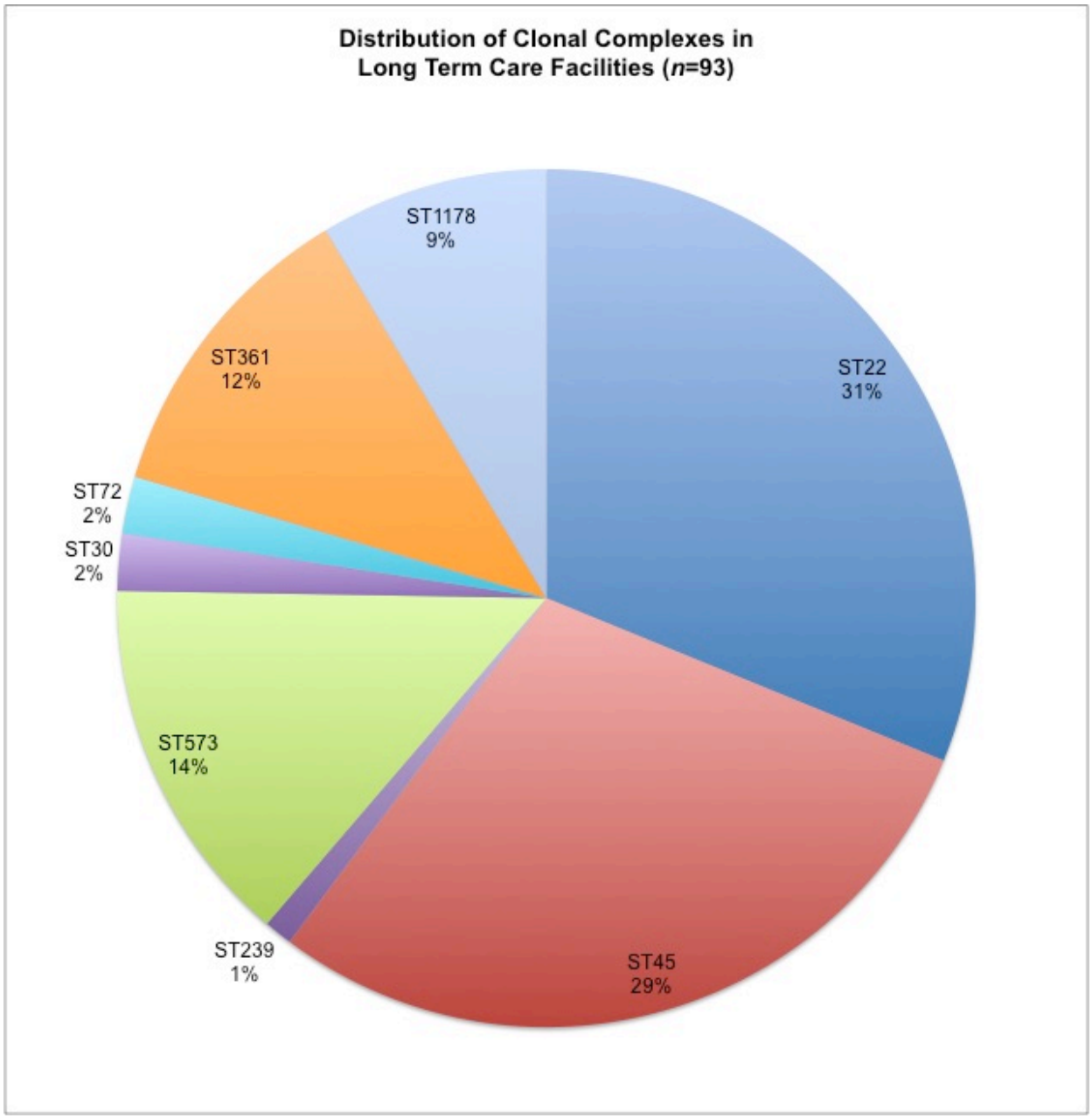


Figure 1-C.


Distribution of Clonal Complexes in
Long Term Care Facilities (n=93)
ST1178
9%
ST22
31%
ST361
12%
ST72
2%
ST30
2%
ST573
14%
ST239
1%
ST45
29%

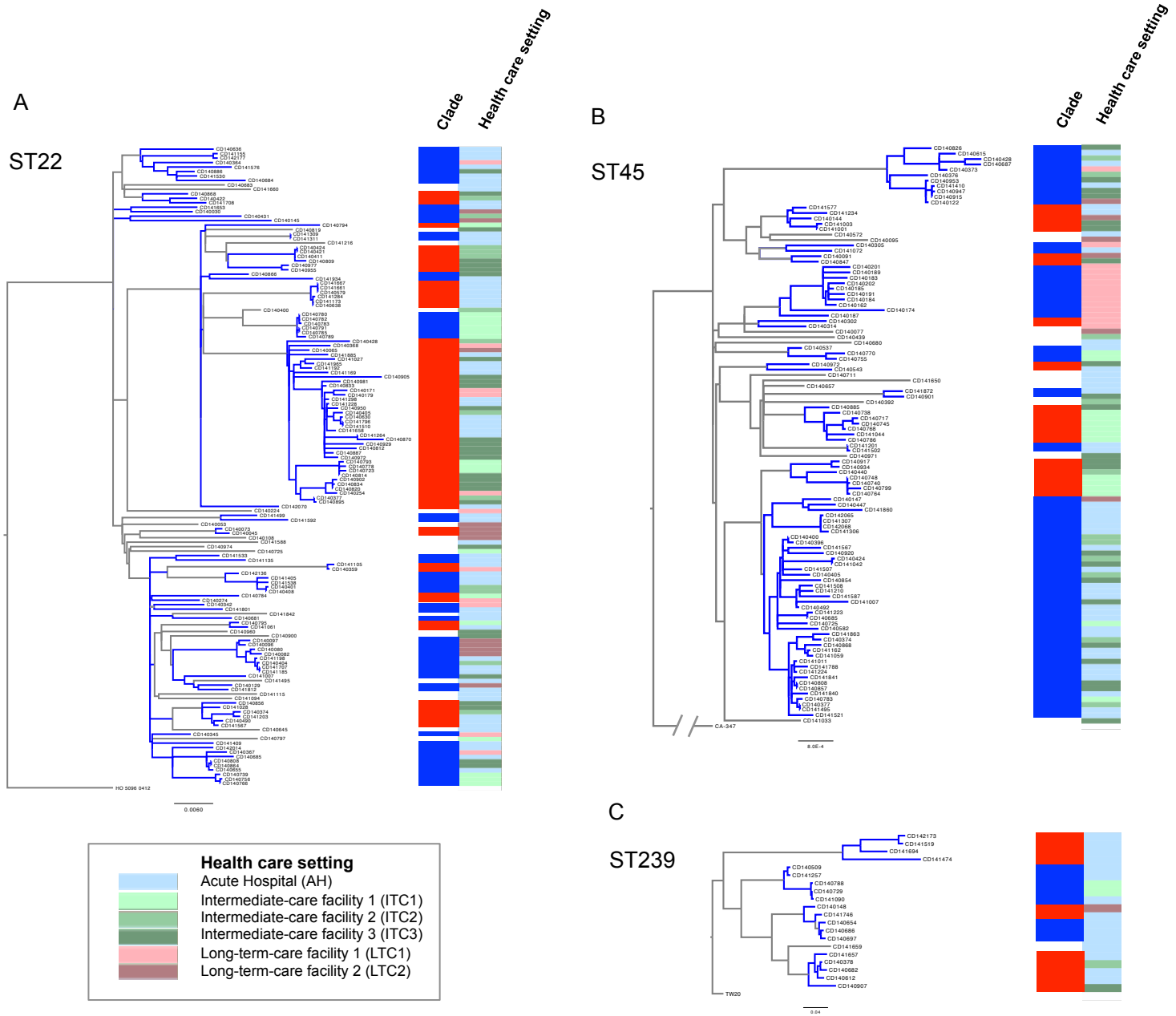
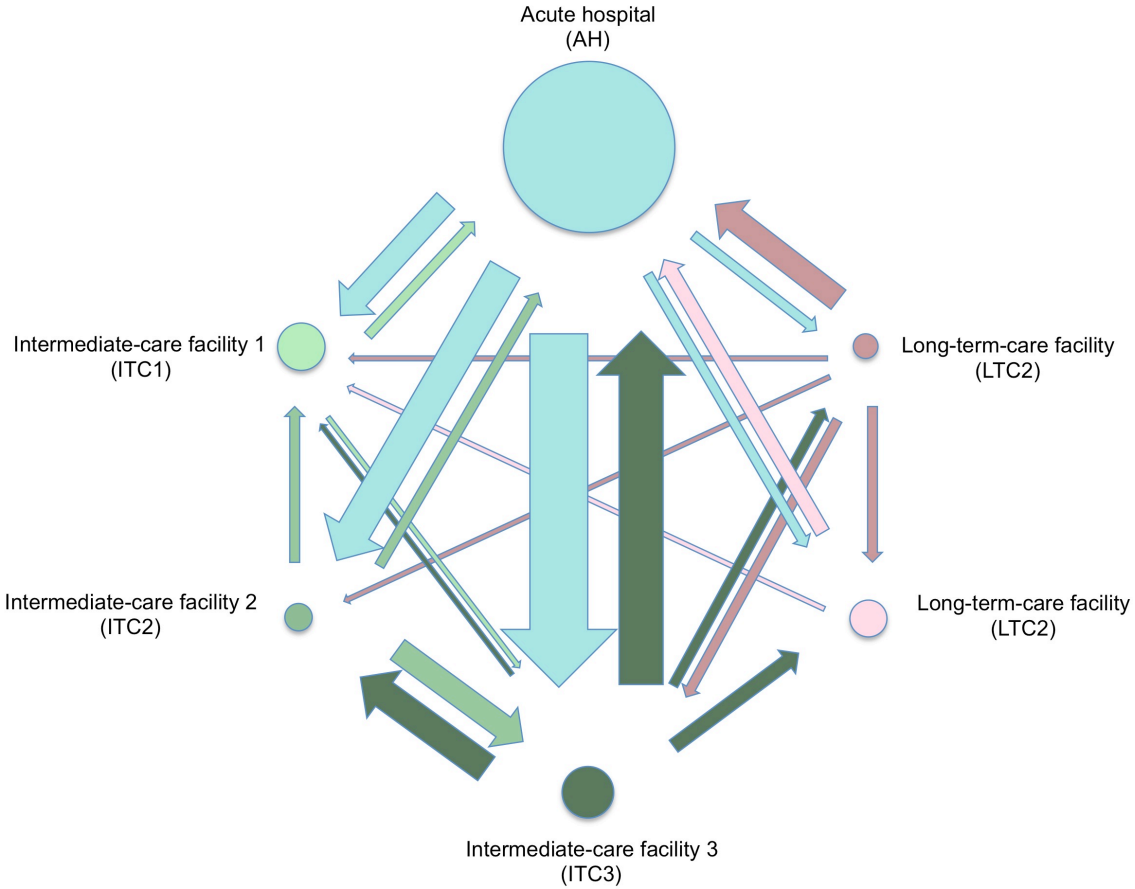

A
ST22
Clade
Health care setting
B
ST45
Clade
Health care setting
C
ST239
Health care setting
Acute Hospital (AH)
Intermediate-care facility 1 (ITC1)
Intermediate-care facility 2 (ITC2)
Intermediate-care facility 3 (ITC3)
Long-term-care facility 1 (LTC1)
Long-term-care facility 2 (LTC2)

Figure 2.

Figure 3.


Acute hospital
(AH)
Intermediate-care facility 1
(ITC1)
Long-term-care facility
(LTC2)
Intermediate-care facility 2
(ITC2)
Long-term-care facility
(LTC2)
Intermediate-care facility 3
(ITC3)