**Supplemental Data and Methods for**

**MRSA Strains with Distinct Accessory Genes Predominate at Different Ages in Cystic Fibrosis**

By

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**Supplemental Data:**

**Supplemental Data 1.** Incident *P. aeruginosa* and *S. aureus* infections in patients with cystic fibrosis at the University of Iowa, 2004 – 2017.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Organism** | Pre-existing Infection, N**Total = 337** | Susceptible Individuals\*, N **Total = 337** | Individuals with Incident Infection, N | % With Incident Infection† |
| *P. aeruginosa* | 172 | 165 | 94 | 57.0% |
| MSSA | 101 | 236 | 161 | 68.2% |
| MRSA | 40 | 297 | 109 | 36.7% |

\*Susceptibility defined as either newborn with CF or negative for the listed organism on respiratory cultures during an individual’s first year of available data. †Number of susceptible individuals is used as denominator.

**Supplemental Data 2.** Annualized incidence of MRSA in CF at the University of Iowa, 2004 – 2017.

|  |  |  |  |
| --- | --- | --- | --- |
| **Year** | **Incident Infections, N** | **Susceptible Individuals, N** | **Incidence, %** |
| 2004 | 8 | 106 | 7.5% |
| 2005 | 8 | 111 | 7.2% |
| 2006 | 11 | 113 | 9.7% |
| 2007 | 7 | 113 | 6.2% |
| 2008 | 10 | 117 | 8.5% |
| 2009 | 6 | 115 | 5.2% |
| 2010 | 9 | 116 | 7.8% |
| 2011 | 7 | 119 | 5.9% |
| 2012 | 8 | 114 | 7.0% |
| 2013 | 6 | 119 | 5.0% |
| 2014 | 10 | 119 | 8.4% |
| 2015 | 5 | 117 | 4.3% |
| 2016 | 8 | 127 | 6.3% |
| 2017 | 6 | 126 | 4.8% |



Supplemental Data 3. Prevalence and incidence of CF pathogens at the University of Iowa, 2004 – 2017. **A.** Annualized prevalence of *S. aureus* and *P. aeruginosa* (% of individuals tested with at least one positive respiratory culture during the calendar year). Purple – composite prevalence of *S. aureus* (either MSSA or MRSA), Green – *P. aeruginosa*, Blue – MSSA, Red – MRSA. The prevalence of MRSA has increased, whereas the prevalence of *P. aeruginosa* and MSSA have both declined (*P* < 0.05). **B.** Annualized incidence of MRSA, calculated as the number of new MRSA infections divided by the number of susceptible individuals during the calendar year. MRSA incidence has slowly decreased (*P* = 0.0284).

**Supplemental Table 4.** List of isolates analyzed in this study linked to subject ID.

| **Subject** | **Isolate** | **MLST** | **Cluster** | **Comment** |
| --- | --- | --- | --- | --- |
| 1 | 20814.063 | 5 | A |  |
| 2 | 20814.071 | 8 | B |  |
| 3 | 20814.057 | 5 | A | No previous known ST5 in this subject. Subject first had ST8 MRSA in Nov 2012. |
| 4 | 20814.054 | 87 | C |  |
| 5 | 20814.061 | 1866 | A |  |
| 6 | 20814.080 | 97 | C | No SCC*mec* element detected. |
| 7 | 20814.006 | 5 | A |  |
| 7 | 20814.043 | novel | A |  |
| 7 | 20814.051 | 5 | A |  |
| 7 | 20814.091 | novel | A |  |
| 8 | 20814.042 | 1750 | B |  |
| 9 | 20814.081 | 105 | A |  |
| 10 | 20814.088 | 5 | A |  |
| 11 | 20814.025 | 105 | A |  |
| 12 | 20814.039 | 105 | A |  |
| 13 | 20814.023 | 5 | A | Deposited as AF1605 in NCBI.Subject had isolate with same ST in July 2015. |
| 13 | 20814.036 | 5 | A |  |
| 14 | 20814.065 | 105 | A |  |
| 15 | 20814.034 | 5 | A |  |
| 15 | 20814.053 | 5 | A |  |
| 16 | 20814.011 | 5 | A |  |
| 17 | 20814.028 | 5 | A | Deposited as AF1720 in NCBI.Subject had isolate with same ST in Aug 2011. |
| 18 | 20814.027 | 5 | A |  |
| 19 | 20814.058 | 105 | A |  |
| 20 | 20814.012 | 5 | A |  |
| 21 | 20814.096 | 8 | B |  |
| 22 | 20814.010 | 5 | A |  |
| 23 | 20814.021 | 8 | B |  |
| 23 | 20814.068 | 8 | B |  |
| 24 | 20814.056 | 59 | C |  |
| 25 | 20814.002 | 5 | A | Subject had isolate with same ST in Sep 2012. |
| 26 | 20814.083 | 5 | A |  |
| 27 | 20814.099 | 5 | A |  |
| 28 | 20814.038 | 5 | A |  |
| 29 | 20814.082 | 5 | A |  |
| 30 | 20814.048 | 8 | B |  |
| 31 | 20814.044 | 5 | A |  |
| 31 | 20814.073 | 5 | A |  |
| 31 | 20814.085 | 5 | A |  |
| 32 | 20814.049 | 105 | A |  |
| 32 | 20814.050 | 105 | A |  |
| 33 | 20814.041 | 5 | A |  |
| 34 | 20814.055 | 8 | B | Subject had isolate with same ST in Oct 2013. |
| 35 | 20814.026 | 105 | A |  |
| 36 | 20814.022 | 5 | A |  |
| 36 | 20814.077 | 5 | A |  |
| 37 | 20814.059 | 8 | B |  |
| 38 | 20814.033 | 5 | A |  |
| 39 | 20814.001 | 5 | A |  |
| 40 | 20814.040 | 5 | A |  |
| 41 | 20814.047 | 2253 | B |  |
| 41 | 20814.072 | 2253 | B |  |
| 42 | 20814.030 | 59 | C |  |
| 43 | 20814.078 | 105 | A |  |
| 44 | 20814.004 | 8 | B |  |
| 44 | 20814.079 | 8 | B |  |
| 45 | 20814.045 | 15 | C | No SCC*mec* element detected. |
| 46 | 20814.046 | 5 | A |  |
| 47 | 20814.005 | 5 | A |  |
| 48 | 20814.029 | 5 | A |  |
| 48 | 20814.076 | 5 | A |  |
| 49 | 20814.013 | 8 | B | Subject had isolate with same ST in May 2013. |
| 50 | 20814.069 | 5 | A |  |
| 50 | 20814.098 | 5 | A |  |
| 51 | 20814.037 | 5 | A |  |
| 52 | 20814.066 | 105 | A | Subject had isolate with same ST in Jan 2015. |
| 52 | 20814.090 | 105 | A | Deposited as AF1667 in NCBI. |
| 52 | 20814.094 | 4234 | A | No SCC*mec* element detected. |
| 53 | 20814.032 | 105 | A |  |
| 54 | 20814.018 | 5 | A | Subject had isolate with same ST in Mar 2015. |
| 55 | 20814.086 | 8 | B | Subject had isolate with same ST in Feb 2010. |
| 56 | 20814.097 | 5 | A |  |
| 57 | 20814.008 | 5 | A |  |
| 57 | 20814.031 | 5 | A |  |
| 58 | 20814.016 | 5 | A |  |
| 59 | 20814.052 | 5 | A |  |
| 59 | 20814.093 | 5 | A |  |
| 60 | 20814.092 | 5 | A |  |
| 61 | 20814.074 | 105 | A |  |
| 62 | 20814.009 | 8 | B | Subject had isolate with same ST in Feb 2013. |
| 62 | 20814.089 | 8 | B |  |
| 63 | 20814.070 | 105 | A |  |
| 64 | 20814.019 | 5 | A |  |
| 64 | 20814.020 | 5 | A |  |
| 64 | 20814.075 | 5 | A |  |
| 65 | 20814.084 | 5 | A |  |
| 65 | 20814.095 | 5 | A |  |
| 66 | 20814.014 | 5 | A |  |
| 66 | 20814.015 | 5 | A |  |
| 67 | 20814.017 | 5 | A |  |
| 68 | 20814.024 | 398 | C | No SCC*mec* element detected. |
| 69 | 20814.067 | 5 | A |  |
| 70 | 20814.003 | 5 | A |  |
| 71 | 20814.087 | 8 | B | Subject had isolate with same ST in July 2016. Subject previously with ST30 MRSA in Oct 2012. |
| 72 | 20814.062 | 5 | A |  |
| 73 | 20814.060 | 5 | A |  |
| 74 | 20814.007 | 8 | B |  |

**Supplemental Data 5.** Phylogenetic analysis of ST8 and related strains.



Lyve-SET Phylogenetic reconstruction for clade 2 reveals closely related strains shared within selected individuals. Isolate numbers and multilocus sequence types are given at right. All isolates carried SCC*mec* IV. Highly related isolates are indicated with a shaded box, colored based on the relationship between patients. The SNP difference between these isolates is given as a number within the shaded box. Tree scale represents substitutions per site.

**Supplemental Data 6.** Mutations in DNA repair genes that may facilitate increased mutation frequency.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Isolate** | **Gene** | **Reference Position\*** | **Variant** | **Protein Change** | **Sequence Depth** | **SNP %** |
| 20814.019 | *mutL* | 1294677 | ins A | p.P340fs | 93 | 97.84% |
|  |  |  |  |  |  |  |
| 20814.023 | *mutL* | 1294678 | del A | p.P340fs | 75 | 100% |
| 20814.036 | *mutL* | 1294678 | del A | p.P340fs | 25 | 95.99% |
|  |  |  |  |  |  |  |
| 20814.038 | *mutL* | 1294678 | del 2 AA | p.P340fs | 86 | 94.76% |
|  |  |  |  |  |  |  |
| 20814.063 | *mutL* | 1294677 | ins A | p.P340fs | 64 | 96.87% |
|  |  |  |  |  |  |  |
| 20814.060 | *mutS* | 1292614 | del 3 ACA | p.Q530del | 42 | 95.23% |
|  |  |  |  |  |  |  |
| 20814.043 | *mutL,* *mutS* |  |  | Full deletions |  |  |
| 20814.091 | *mutL,* *mutS* |  |  | Full deletions |  |  |

\* sequences are named relative to the Refence Genome N315 (NC\_002745.2).

**Supplemental Data 7.** Genetic basis for erythromycin resistance

| **Isolate** | **Cluster** | **Erythromycin MIC** | **Mykrobe Prediction** | **Erythromycin Resistance Mechanism** **Gene : %Coverage : Depth** |
| --- | --- | --- | --- | --- |
| 20814-001 | A | >=8 | R | *ermA*:100:171 |
| 20814-002 | A | >=8 | R | *ermA*:100:114 |
| 20814-003 | A | >=8 | R | *ermA*:100:192 |
| 20814-004 | B | >=8 | R | *msrA*:100:184 |
| 20814-005 | A | >=8 | R | *ermA*:100:131 |
| 20814-006 | A | >=8 | R | *ermA*:100:212 |
| 20814-007 | B | >=8 | R | *msrA*:100:103 |
| 20814-008 | A | >=8 | R | *ermA*:100:186 |
| 20814-009 | B | >=8 | R | *msrA*:100:176 |
| 20814-010 | A | >=8 | R | *ermA*:100:159 |
| 20814-011 | A | >=8 | R | *ermA*:100:320 |
| 20814-012 | A | >=8 | R | *ermA*:100:141 |
| 20814-013 | B | >=8 | R | *msrA*:100:143 |
| 20814-014 | A | >=8 | R | *ermA*:100:106*ermC*:92:30 |
| 20814-015 | A | >=8 | R | *ermA*:100:182 |
| 20814-016 | A | >=8 | R | *ermA*:100:163 |
| 20814-017 | A | >=8 | R | *ermA*:100:99 |
| 20814-018 | A | >=8 | R | *ermA*:100:153 |
| 20814-019 | A | >=8 | R | *ermA*:100:161 |
| 20814-020 | A | >=8 | R | *ermA*:100:98 |
| 20814-021 | B | >=8 | R | *ermC*:100:121 |
| 20814-022 | A | >=8 | R | *ermA*:100:85 |
| 20814-023 | A | >=8 | R | *ermA*:100:203 |
| 20814-024 | C | 0.5 | R | *ermA*:100:35 |
| 20814-025 | A | >=8 | R | *ermA*:100:91 |
| 20814-026 | A | >=8 | R | *ermA*:100:171*ermC*:100:2929 |
| 20814-027 | A | >=8 | R | *ermA*:100:93 |
| 20814-028 | A | >=8 | R | *ermA*:100:167 |
| 20814-029 | A | >=8 | R | *ermA*:100:83 |
| 20814-030 | C | >=8 | S |  |
| 20814-031 | A | >=8 | R | *ermA*:100:81 |
| 20814-032 | A | >=8 | R | *ermA*:100:109 |
| 20814-033 | A | >=8 | R | *ermA*:100:183 |
| 20814-034 | A | >=8 | R | *ermA*:100:254 |
| 20814-036 | A | >=8 | R | *ermA*:100:100 |
| 20814-037 | A | >=8 | R | *ermA*:100:73 |
| 20814-038 | A | >=8 | R | *ermA*:100:208 |
| 20814-039 | A | >=8 | R | *ermA*:100:165*msrA*:100:115 |
| 20814-040 | A | >=8 | R | *ermA*:100:176 |
| 20814-041 | A | >=8 | R | *ermA*:100:95*ermC*:92:25 |
| 20814-042 | B | >=8 | R | *msrA*:100:128 |
| 20814-043 | A | 4 | R | *ermA*:100:178 |
| 20814-044 | A | >=8 | R | *ermA*:100:192 |
| 20814-045 | C | >=8 | S |  |
| 20814-046 | A | >=8 | R | *ermA*:100:79 |
| 20814-047 | B | <0.25 | S |  |
| 20814-048 | B | >=8 | R | *msrA*:100:126 |
| 20814-049 | A | >=8 | R | *ermA*:100:91 |
| 20814-050 | A | >=8 | R | *ermA*:100:102*ermC*:92:52*msrA*:100:127 |
| 20814-051 | A | >=8 | R | *ermA*:100:163 |
| 20814-052 | A | >=8 | R | *ermA*:100:139 |
| 20814-053 | A | >=8 | R | *ermA*:100:93 |
| 20814-054 | C | >=8 | R | *msrA*:100:144 |
| 20814-055 | B | >=8 | R | *msrA*:100:118 |
| 20814-056 | C | >=8 | R | *msrA*:100:126 |
| 20814-057 | A | <0.25 | S |  |
| 20814-058 | A | >=8 | R | *ermA*:100:135*msrA*:100:158 |
| 20814-059 | B | >=8 | R | *msrA*:100:100 |
| 20814-060 | A | >=8 | R | *ermA*:100:120 |
| 20814-061 | A | >=8 | R | *ermC*:99:2272 |
| 20814-062 | A | >=8 | R | *ermA*:100:95 |
| 20814-063 | A | >=8 | R | *ermA*:100:154 |
| 20814-065 | A | >=8 | R | *ermA*:100:70*ermC*:100:430*msrA*:100:132 |
| 20814-066 | A | >=8 | R | *ermA*:100:104*ermC*:100:376*msrA*:100:134 |
| 20814-067 | A | >=8 | R | *ermA*:100:136 |
| 20814-068 | B | >=8 | R | *ermC*:100:109 |
| 20814-069 | A | >=8 | R | *ermA*:100:154 |
| 20814-070 | A | >=8 | R | *ermA*:100:169 |
| 20814-071 | A | >=8 | R | *msrA*:100:148 |
| 20814-072 | B | >=8 | R | *ermC*:97:2185 |
| 20814-073 | A | >=8 | R | *ermA*:100:165 |
| 20814-074 | A | >=8 | R | *ermA*:100:149*msrA*:99:114 |
| 20814-075 | A | >=8 | R | *ermA*:100:156 |
| 20814-076 | A | >=8 | R | *ermA*:100:64 |
| 20814-077 | A | >=8 | R | *ermA*:100:144 |
| 20814-078 | A | >=8 | R | *ermA*:100:154 |
| 20814-079 | B | >=8 | R | *msrA*:100:99 |
| 20814-080 | C | >=8 | S |  |
| 20814-081 | A | >=8 | R | *ermA*:100:287*msrA*:100:136 |
| 20814-082 | A | >=8 | R | *ermA*:100:151 |
| 20814-083 | A | >=8 | S |  |
| 20814-084 | A | >=8 | R | *ermA*:100:190 |
| 20814-085 | A | >=8 | R | *ermA*:100:202 |
| 20814-086 | B | >=8 | R | *msrA*:100:122 |
| 20814-087 | B | >=8 | R | *msrA*:100:123 |
| 20814-088 | A | >=8 | R | *ermA*:100:163 |
| 20814-089 | B | 0.5 | S |  |
| 20814-090 | A | >=8 | R | *ermA*:100:174*ermC*:100:3417*msrA*:100:98 |
| 20814-091 | A | 4 | R | *ermA*:100:145 |
| 20814-092 | A | >=8 | R | *ermA*:100:97 |
| 20814-093 | A | >=8 | R | *ermA*:100:114 |
| 20814-094 | A | >=8 | R | *msrA*:100:76 |
| 20814-095 | A | >=8 | R | *ermA*:100:138 |
| 20814-096 | A | NA | R | *msrA*:100:150 |
| 20814-097 | A | >=8 | R | *ermA*:100:94 |
| 20814-098 | A | >=8 | R | *ermA*:100:167 |
| 20814-099 | A | >=8 | R | *ermA*:100:94 |

**Supplemental Data 8.** Genetic basis for ciprofloxacin resistance

| **Isolate** | **Cluster** | **Cipro MIC** | **Mykrobe Prediction** | **Ciprofloxacin resistance mutations**gene\_AA variant - Kmers : Ref Kmer count : Alt Kmer count : Confidence |
| --- | --- | --- | --- | --- |
| 20814-001 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:106:1662:8509*grlA*\_S80F-TCC1419997TTC:67:1073:6257 |
| 20814-002 | A | >=8 | S |  |
| 20814-003 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:96:1527:7940 |
| 20814-004 | B | >=8 | R | *gyrA*\_S84L-TCA7254TTA:105:1628:8120*grlA*\_S80Y-TCC1419997TAC:59:905:5488 |
| 20814-005 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:182:2874:12846*grlA*\_S80F-TCC1419997TTC:81:1414:7282 |
| 20814-006 | A | 1 | S |  |
| 20814-007 | B | >=8 | R | *gyrA*\_S84L-TCA7254TTA:72:1128:6234*grlA*\_S80Y-TCC1419997TAC:69:1103:6144 |
| 20814-008 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:109:1724:8779 |
| 20814-009 | B | 1 | S |  |
| 20814-010 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:94:1485:7491 |
| 20814-011 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:106:1660:8558*grlA*\_S80F-TCC1419997TTC:71:1182:6744 |
| 20814-012 | A | >=8 | S |  |
| 20814-013 | B | <=0.5 | S |  |
| 20814-014 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:146:2307:10501*grlA*\_S80F-TCC1419997TTC:104:1751:8396 |
| 20814-015 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:127:1970:9712*grlA*\_S80F-TCC1419997TTC:73:1171:6662 |
| 20814-016 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:119:1882:9328*grlA*\_S80F-TCC1419997TTC:68:1092:6302 |
| 20814-017 | A | >=8 | S |  |
| 20814-018 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:80:1305:6983*grlA*\_S80F-TCC1419997TTC:57:926:5525 |
| 20814-019 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:96:1553:7961 |
| 20814-020 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:130:2098:9625 |
| 20814-021 | B | >=8 | R | *gyrA*\_S84L-TCA7254TTA:77:1211:6781*grlA*\_S80Y-TCC1419997TAC:80:1265:6990 |
| 20814-022 | A | >=8 | S |  |
| 20814-023 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:123:1948:9781*grlA*\_S80F-TCC1419997TTC:93:1506:8095 |
| 20814-024 | C | <=0.5 | S |  |
| 20814-025 | A | >=8 | S |  |
| 20814-026 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:105:1603:8043 |
| 20814-027 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:163:2518:11009*grlA*\_S80F-TCC1419997TTC:70:1107:5614 |
| 20814-028 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:112:1785:9016*grlA*\_S80F-TCC1419997TTC:90:1414:7588 |
| 20814-029 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:105:1629:8463*grlA*\_S80Y-TCC1419997TAC:80:1298:7211 |
| 20814-030 | C | <=0.5 | S |  |
| 20814-031 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:130:2102:9470 |
| 20814-032 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:146:2317:10321 |
| 20814-033 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:135:2126:10404 |
| 20814-034 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:77:1209:6630*grlA*\_S80F-TCC1419997TTC:77:1237:6745 |
| 20814-036 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:157:2519:11380*grlA*\_S80F-TCC1419997TTC:94:1599:7872 |
| 20814-037 | A | >=8 | S |  |
| 20814-038 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:117:1849:9343*grlA*\_S80F-TCC1419997TTC:78:1306:7280 |
| 20814-039 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:121:1832:8769 |
| 20814-040 | A | >=8 | S |  |
| 20814-041 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:132:2077:9559*grlA*\_S80F-TCC1419997TTC:89:1427:7074 |
| 20814-042 | B | >=8 | R | *gyrA*\_S84L-TCA7254TTA:93:1409:7352*grlA*\_S80Y-TCC1419997TAC:72:1094:6294 |
| 20814-043 | A | 4 | S |  |
| 20814-044 | A | >=8 | S |  |
| 20814-045 | C | >=8 | R | *grlA*\_E84G-GAA1420009GGA:81:1221:6834 |
| 20814-046 | A | >=8 | S |  |
| 20814-047 | B | >=8 | R | *gyrA*\_S84L-TCA7254TTA:101:1561:8048*grlA*\_S80F-TCC1419997TTC:69:1144:6625 |
| 20814-048 | B | >=8 | R | *gyrA*\_S84L-TCA7254TTA:65:1061:6074*grlA*\_S80Y-TCC1419997TAC:57:872:5333 |
| 20814-049 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:157:2540:11152*grlA*\_S80Y-TCC1419997TAC:1:1183:6236 |
| 20814-050 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:135:2060:9034 |
| 20814-051 | A | >=8 | S |  |
| 20814-052 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:182:2831:12555*grlA*\_S80F-TCC1419997TTC:94:1479:7381 |
| 20814-053 | A | >=8 | S |  |
| 20814-054 | C | <0.5 | S |  |
| 20814-055 | B | <0.5 | S |  |
| 20814-056 | C | <0.5 | S |  |
| 20814-057 | A | <0.5 | S |  |
| 20814-058 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:202:3233:14462 |
| 20814-059 | B | >=8 | R | *gyrA*\_S84L-TCA7254TTA:88:1386:7053*grlA*\_S80Y-TCC1419997TAC:48:788:4769 |
| 20814-060 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:143:2299:10651 |
| 20814-061 | A | <0.5 | S |  |
| 20814-062 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:136:2080:9270*grlA*\_S80F-TCC1419997TTC:84:1293:6261 |
| 20814-063 | A | >=8 | S |  |
| 20814-065 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:161:2522:11091 |
| 20814-066 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:141:2233:10161 |
| 20814-067 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:96:1538:7700*grlA*\_S80F-TCC1419997TTC:55:899:5252 |
| 20814-068 | B | >=8 | R | *gyrA*\_S84L-TCA7254TTA:105:1642:8345*grlA*\_S80Y-TCC1419997TAC:81:1297:7031 |
| 20814-069 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:92:1416:7416*grlA*\_S80F-TCC1419997TTC:76:1223:6692 |
| 20814-070 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:127:1769:6722 |
| 20814-071 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:115:1791:8401*grlA*\_S80Y-TCC1419997TAC:124:2034:9359 |
| 20814-072 | B | >=8 | R | *gyrA*\_S84L-TCA7254TTA:72:1150:6067*grlA*\_S80F-TCC1419997TTC:62:1023:5588 |
| 20814-073 | A | >=8 | S |  |
| 20814-074 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:84:1279:6717 |
| 20814-075 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:90:1400:7159*grlA*\_E84G-GAA1420009GGA:62:797:4682 |
| 20814-076 | A | NA | R | *gyrA*\_S84L-TCA7254TTA:90:1430:7510*grlA*\_S80Y-TCC1419997TAC:73:1184:6573 |
| 20814-077 | A | >=8 | S |  |
| 20814-078 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:116:1816:9184 |
| 20814-079 | B | >=8 | R | *gyrA*\_S84L-TCA7254TTA:71:1150:6328*grlA*\_S80Y-TCC1419997TAC:60:952:5562 |
| 20814-080 | C | <0.5 | S |  |
| 20814-081 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:106:1636:8459 |
| 20814-082 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:90:1396:7258*grlA*\_S80F-TCC1419997TTC:69:1126:6380 |
| 20814-083 | A | <0.5 | S |  |
| 20814-084 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:115:1788:8931*grlA*\_S80F-TCC1419997TTC:64:1029:6032 |
| 20814-085 | A | >=8 | S |  |
| 20814-086 | B | <0.5 | S |  |
| 20814-087 | B | >=8 | R | *gyrA*\_S84L-TCA7254TTA:91:1388:7391*grlA*\_S80Y-TCC1419997TAC:75:1148:6474 |
| 20814-088 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:118:1832:8927 |
| 20814-089 | B | 1 | S |  |
| 20814-090 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:131:1834:6972 |
| 20814-091 | A | 4 | S |  |
| 20814-092 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:133:2038:9253*grlA*\_S80F-TCC1419997TTC:69:1102:5683 |
| 20814-093 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:148:2271:10288*grlA*\_S80F-TCC1419997TTC:116:1665:6341 |
| 20814-094 | A | >=8 | S |  |
| 20814-095 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:90:1422:7192*grlA*\_S80F-TCC1419997TTC:60:945:5363 |
| 20814-096 | A | NA | R | *gyrA*\_S84L-TCA7254TTA:147:2042:7758*grlA*\_S80Y-TCC1419997TAC:99:1646:7958 |
| 20814-097 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:121:1884:8729 |
| 20814-098 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:89:1429:7425*grlA*\_S80F-TCC1419997TTC:63:1064:6037 |
| 20814-099 | A | >=8 | R | *gyrA*\_S84L-TCA7254TTA:169:2611:11324*grlA*\_S80F-TCC1419997TTC:96:1522:7378 |

**Supplemental Data 9.** Genes identified by HISAT2 in isolates belonging to Cluster A

|  |  | **Isolates per cluster** |  |
| --- | --- | --- | --- |
| **Inference** | **Locus** | **A** | **B** | **C** | **Product** |
| WP\_000952924.1 | SA\_RS00340 | 69 | 0 | 0 | beta-lactam sensor/signal transducer MecR1 |
| WP\_001242578.1 | SA\_RS00305 | 67 | 0 | 0 | bleomycin binding protein |
| WP\_019468540.1 | SAR\_RS00225 | 69 | 0 | 0 | dihydroneopterin aldolase |
| WP\_000527474.1 | SA\_RS15115 | 73 | 0 | 0 | DUF1542 domain-containing protein |
| WP\_000708247.1 | SAR\_RS15270 | 73 | 0 | 0 | DUF1829 domain-containing protein |
| WP\_000762519.1 | SA\_RS10335 | 57 | 0 | 0 | DUF2513 domain-containing protein |
| WP\_001795146.1 | SAS\_RS14535 | 69 | 0 | 0 | DUF3125 domain-containing protein |
| WP\_000882118.1 | SAHV\_RS03175 | 72 | 0 | 0 | DUF443 domain-containing protein |
| WP\_000226989.1 | SA\_RS03215 | 73 | 0 | 0 | DUF443 family protein |
| WP\_001806402.1 | SA\_RS10330 | 57 | 0 | 0 | DUF771 domain-containing protein |
| WP\_000411461.1 | SA\_RS00510 | 69 | 0 | 0 | DUF927 domain-containing protein |
| WP\_001557397.1 | SAHV\_RS09675 | 72 | 0 | 0 | enterotoxin |
| WP\_001557395.1 | SAHV\_RS09670 | 70 | 0 | 0 | enterotoxin |
| WP\_000935737.1 | SAR\_RS09820 | 73 | 0 | 0 | exotoxin |
| WP\_000841404.1 | SAS\_RS12995 | 68 | 0 | 0 | fibronectin-binding protein FnbB |
| WP\_001557499.1 | SAHV\_RS15235 | 73 | 0 | 0 | HNH endonuclease |
| WP\_010922836.1 | SA\_RS15120 | 73 | 0 | 0 | hyperosmolarity resistance protein Ebh |
| WP\_001557364.1 | SAHV\_RS08480 | 73 | 0 | 0 | hypothetical protein |
| WP\_001791631.1 | SAHV\_RS15100 | 73 | 0 | 0 | hypothetical protein |
| WP\_001800651.1 | SAHV\_RS15250 | 73 | 0 | 0 | hypothetical protein |
| WP\_016170465.1 | SAHV\_RS04875 | 73 | 0 | 0 | hypothetical protein |
| WP\_001799173.1 | SAHV\_RS14880 | 72 | 0 | 0 | hypothetical protein |
| WP\_001627778.1 | SAS\_RS03015 | 71 | 0 | 0 | hypothetical protein |
| NP\_763595.1 | SA\_RS00450 | 70 | 0 | 0 | hypothetical protein |
| WP\_001060127.1 | SAR\_RS00310 | 70 | 0 | 0 | hypothetical protein |
| WP\_001797999.1 | SAR\_RS15290 | 70 | 0 | 0 | hypothetical protein |
| WP\_000626133.1 | SA\_RS00505 | 69 | 0 | 0 | hypothetical protein |
| WP\_001176969.1 | SA\_RS00520 | 69 | 0 | 0 | hypothetical protein |
| WP\_001193834.1 | SA\_RS00515 | 69 | 0 | 0 | hypothetical protein |
| WP\_001795283.1 | SAR\_RS14740 | 69 | 0 | 0 | hypothetical protein |
| WP\_002502216.1 | SACOL\_RS00215 | 69 | 0 | 0 | hypothetical protein |
| WP\_002505017.1 | SAR\_RS00280 | 69 | 0 | 0 | hypothetical protein |
| WP\_000435352.1 | SAR\_RS07975 | 58 | 0 | 0 | hypothetical protein |
| WP\_000777474.1 | SAR\_RS15380 | 73 | 0 | 0 | IS21 family transposase |
| WP\_001606479.1 | USA300HOU\_RS09940 | 66 | 0 | 0 | ISL3 family transposase |
| WP\_000852430.1 | SA\_RS00495 | 69 | 0 | 0 | K(+)-transporting ATPase subunit B |
| WP\_001646386.1 | SAV\_RS00500 | 69 | 0 | 0 | K(+)-transporting ATPase subunit C |
| WP\_000631574.1 | SA\_RS00485 | 69 | 0 | 0 | K(+)-transporting ATPase subunit F |
| WP\_000369216.1 | SA\_RS00345 | 69 | 0 | 0 | mecA-type methicillin resistance repressor MecI |
| YP\_499449.1 | SAS\_RS14955 | 71 | 0 | 0 | nitrogen fixation protein NifR |
| WP\_014532405.1 | SA\_RS15045 | 69 | 0 | 0 | phenol-soluble modulin PSM-mec |
| WP\_001619005.1 | SAR\_RS00160 | 67 | 0 | 0 | Plasmid recombination enzyme type 2 |
| YP\_003028729.1 | SA\_RS00300 | 67 | 0 | 0 | Plasmid recombination enzyme type 2 |
| WP\_002460931.1 | SA\_RS00490 | 69 | 0 | 0 | potassium-transporting ATPase subunit A |
| WP\_001001347.1 | SA\_RS00525 | 69 | 0 | 0 | protein kinase |
| WP\_001611915.1 | SA\_RS00295 | 67 | 0 | 0 | protein rep |
| WP\_000659046.1 | SA\_RS00410 | 69 | 0 | 0 | RadC family protein |
| WP\_001817892.1 | SA\_RS15040 | 67 | 0 | 0 | replication family protein |
| WP\_000858967.1 | SA\_RS00475 | 69 | 0 | 0 | response regulator transcription factor |
| WP\_001643603.1 | SAR\_RS00210 | 69 | 0 | 0 | ROK family transcriptional regulator |
| WP\_010922808.1 | SA\_RS00350 | 69 | 0 | 0 | ROK family transcriptional regulator |
| WP\_000446429.1 | SA\_RS00480 | 69 | 0 | 0 | sensor histidine kinase KdpD |
| WP\_000273824.1 | SA\_RS00445 | 71 | 0 | 0 | single-stranded DNA-binding protein |
| WP\_000736706.1 | SAR\_RS09795 | 71 | 0 | 0 | staphylococcal enterotoxin type G |
| WP\_000713847.1 | SAR\_RS09810 | 71 | 0 | 0 | staphylococcal enterotoxin type I |
| WP\_000821661.1 | SAR\_RS09815 | 73 | 0 | 0 | staphylococcal enterotoxin type M |
| WP\_000350222.1 | SA\_RS00375 | 69 | 0 | 0 | sulfite exporter TauE/SafE family protein |
| WP\_000542365.1 | SA\_RS02280 | 73 | 0 | 0 | tandem-type lipoprotein |
| WP\_001594677.1 | SAR\_RS02175 | 73 | 0 | 0 | tandem-type lipoprotein |
| WP\_001557593.1 | SAHV\_RS02265 | 72 | 0 | 0 | tandem-type lipoprotein |
| WP\_001557596.1 | SA\_RS02295 | 72 | 0 | 0 | tandem-type lipoprotein |
| WP\_001578691.1 | SAHV\_RS02270 | 72 | 0 | 0 | tandem-type lipoprotein |
| WP\_001667477.1 | SAR\_RS02195 | 72 | 0 | 0 | tandem-type lipoprotein |
| WP\_001802015.1 | SA\_RS02300 | 71 | 0 | 0 | tandem-type lipoprotein |
| WP\_000972654.1 | SAHV\_RS13440 | 62 | 0 | 0 | tandem-type lipoprotein |
| WP\_001813970.1 | SAR\_RS02180 | 73 | 0 | 0 | tandem-type lipoprotein Lpl1 |
| WP\_017328575.1 | SAB\_RS00145 | 65 | 0 | 0 | tRNA-dihydrouridine synthase |
| WP\_002464589.1 | SAR\_RS02150 | 65 | 0 | 0 | type I restriction-modification system subunit |
| WP\_001628779.1 | SA\_RS04230 | 73 | 0 | 0 | von Willebrand factor binding protein Vwb |
| WP\_000535897.1 | SAR\_RS00325 | 69 | 0 | 0 | YfcC family protein |

**Supplemental Data 10.** Genes identified by HISAT2 in isolates belonging to Cluster B

|  |  | **Isolates per cluster** |  |
| --- | --- | --- | --- |
| **Inference** | **Locus** | **A** | **B** | **C** | **Product** |
| WP\_011274479.1 | SAUSA300\_RS00385 | 0 | 15 | 0 | ABC transporter ATP-binding protein |
| WP\_002469402.1 | SAUSA300\_RS00380 | 0 | 15 | 0 | ABC transporter permease |
| WP\_019165742.1 | SAUSA300\_RS00375 | 0 | 15 | 0 | ABC transporter permease |
| WP\_002491360.1 | SAUSA300\_RS00355 | 0 | 15 | 0 | alpha/beta hydrolase |
| NP\_763660.1 | SAUSA300\_RS00325 | 0 | 15 | 0 | arginine-ornithine antiporter |
| NP\_763662.1 | SAUSA300\_RS00335 | 0 | 15 | 0 | ArgR family transcriptional regulator |
| WP\_016930504.1 | SAUSA300\_RS00390 | 0 | 15 | 0 | ATP-binding cassette domain-containing protein |
| YP\_500940.1 | SACOL\_RS11590 | 0 | 18 | 0 | ATP-dependent Clp protease ATP-binding subunit |
| NP\_763657.1 | SAUSA300\_RS00310 | 0 | 15 | 0 | carbamate kinase |
| WP\_011274475.1 | SAUSA300\_RS00365 | 0 | 15 | 0 | class I SAM-dependent methyltransferase |
| NP\_763681.1 | SAUSA300\_RS00395 | 0 | 15 | 0 | copper-translocating P-type ATPase |
| NP\_763659.1 | SAUSA300\_RS00320 | 0 | 15 | 0 | Crp/Fnr family transcriptional regulator |
| WP\_019835852.1 | SAUSA300\_RS00400 | 0 | 15 | 0 | DUF1541 domain-containing protein |
| WP\_012086592.1 | SAS\_RS00155 | 0 | 15 | 0 | DUF1643 domain-containing protein |
| YP\_500025.1 | SACOL\_RS07790 | 0 | 18 | 0 | DUF1672 domain-containing protein |
| WP\_020444682.1 | SACOL\_RS07800 | 0 | 16 | 0 | DUF1672 domain-containing protein |
| YP\_498651.1 | SACOL\_RS00375 | 0 | 18 | 0 | DUF4865 family protein |
| YP\_500444.1 | SACOL\_RS09595 | 0 | 18 | 0 | DUF4888 domain-containing protein |
| YP\_498848.1 | SACOL\_RS01360 | 0 | 18 | 0 | DUF5079 family protein |
| YP\_500449.1 | SACOL\_RS09620 | 0 | 18 | 0 | enterotoxin |
| YP\_500452.1 | SACOL\_RS09635 | 0 | 18 | 0 | gallidermin/nisin family lantibiotic |
| YP\_500731.1 | SACOL\_RS10505 | 0 | 17 | 0 | GNAT family N-acetyltransferase |
| NP\_763581.1 | SAUSA300\_RS00275 | 0 | 15 | 0 | GNAT family N-acetyltransferase |
| WP\_000027972.1 | SAUSA300\_RS00250 | 0 | 15 | 0 | HNH endonuclease |
| WP\_000188802.1 | SAUSA300\_RS09520 | 0 | 18 | 0 | hypothetical protein |
| WP\_000365049.1 | SACOL\_RS11595 | 0 | 18 | 0 | hypothetical protein |
| WP\_000905716.1 | SAUSA300\_RS00790 | 0 | 18 | 0 | hypothetical protein |
| WP\_001550008.1 | SAS\_RS00620 | 0 | 18 | 0 | hypothetical protein |
| WP\_001791482.1 | SAS\_RS14670 | 0 | 18 | 0 | hypothetical protein |
| WP\_001793241.1 | SAS\_RS14325 | 0 | 18 | 0 | hypothetical protein |
| WP\_001793432.1 | SAS\_RS09490 | 0 | 18 | 0 | hypothetical protein |
| WP\_001803175.1 | USA300HOU\_RS15820 | 0 | 18 | 0 | hypothetical protein |
| WP\_014532651.1 | SACOL\_RS14785 | 0 | 18 | 0 | hypothetical protein |
| YP\_498711.1 | SACOL\_RS00675 | 0 | 18 | 0 | hypothetical protein |
| YP\_498992.1 | SACOL\_RS02465 | 0 | 18 | 0 | hypothetical protein |
| YP\_499827.1 | SACOL\_RS06815 | 0 | 18 | 0 | hypothetical protein |
| YP\_499831.1 | SACOL\_RS06835 | 0 | 18 | 0 | hypothetical protein |
| YP\_499832.1 | SACOL\_RS06840 | 0 | 18 | 0 | hypothetical protein |
| YP\_500024.1 | SACOL\_RS07785 | 0 | 18 | 0 | hypothetical protein |
| YP\_500423.1 | SACOL\_RS09490 | 0 | 18 | 0 | hypothetical protein |
| YP\_500445.1 | SACOL\_RS14780 | 0 | 18 | 0 | hypothetical protein |
| YP\_500886.1 | SACOL\_RS14870 | 0 | 18 | 0 | hypothetical protein |
| YP\_500937.1 | SACOL\_RS11575 | 0 | 18 | 0 | hypothetical protein |
| YP\_500943.1 | SACOL\_RS11600 | 0 | 18 | 0 | hypothetical protein |
| YP\_500944.1 | SACOL\_RS11605 | 0 | 18 | 0 | hypothetical protein |
| YP\_501312.1 | SACOL\_RS13395 | 0 | 18 | 0 | hypothetical protein |
| YP\_501314.1 | SACOL\_RS13405 | 0 | 18 | 0 | hypothetical protein |
| YP\_501367.1 | SACOL\_RS13660 | 0 | 18 | 0 | hypothetical protein |
| WP\_001570390.1 | SAA6008\_RS12295 | 0 | 17 | 0 | hypothetical protein |
| WP\_001797573.1 | SAUSA300\_RS10880 | 0 | 17 | 0 | hypothetical protein |
| YP\_500732.1 | SACOL\_RS10510 | 0 | 17 | 0 | hypothetical protein |
| YP\_500939.1 | SACOL\_RS11585 | 0 | 17 | 0 | hypothetical protein |
| NP\_763586.1 | SAUSA300\_RS00295 | 0 | 15 | 0 | hypothetical protein |
| WP\_000291518.1 | SAUSA300\_RS00255 | 0 | 15 | 0 | hypothetical protein |
| WP\_000549549.1 | SAUSA300\_RS10780 | 0 | 15 | 0 | hypothetical protein |
| WP\_000957729.1 | SAS\_RS04775 | 0 | 15 | 0 | hypothetical protein |
| WP\_001825326.1 | SAUSA300\_RS07815 | 0 | 15 | 0 | hypothetical protein |
| WP\_002434137.1 | SAUSA300\_RS00285 | 0 | 15 | 0 | hypothetical protein |
| WP\_002434158.1 | SAUSA300\_RS00265 | 0 | 15 | 0 | hypothetical protein |
| WP\_002470711.1 | SAUSA300\_RS00260 | 0 | 15 | 0 | hypothetical protein |
| WP\_002502220.1 | SAUSA300\_RS15700 | 0 | 15 | 0 | hypothetical protein |
| WP\_019835102.1 | SAUSA300\_RS15695 | 0 | 15 | 0 | hypothetical protein |
| YP\_500424.1 | SACOL\_RS09495 | 0 | 18 | 0 | ImmA/IrrE family metalloendopeptidase |
| WP\_016913246.1 | SAUSA300\_RS00360 | 0 | 15 | 0 | IS110 family transposase |
| YP\_500450.1 | SACOL\_RS09625 | 0 | 18 | 0 | lanthionine synthetase C family protein |
| YP\_500451.1 | SACOL\_RS09630 | 0 | 18 | 0 | lantibiotic dehydratase |
| YP\_500446.1 | SACOL\_RS09605 | 0 | 18 | 0 | lantibiotic immunity ABC transporter MutE/EpiE |
| YP\_500447.1 | SACOL\_RS09610 | 0 | 18 | 0 | lantibiotic protection ABC transporter |
| YP\_498652.1 | SACOL\_RS00380 | 0 | 17 | 0 | LysR family transcriptional regulator |
| WP\_001060483.1 | SACOL\_RS03145 | 0 | 15 | 0 | MSCRAMM family adhesin SdrC |
| WP\_000747558.1 | SAUSA300\_RS00370 | 0 | 15 | 0 | nickel ABC transporter substrate-binding |
| NP\_763658.1 | SAUSA300\_RS00315 | 0 | 15 | 0 | ornithine carbamoyltransferase |
| WP\_001805404.1 | SACOL\_RS00665 | 0 | 18 | 0 | replication initiation protein |
| YP\_498709.1 | SAS\_RS00615 | 0 | 18 | 0 | replication initiation protein |
| YP\_500433.1 | SACOL\_RS09545 | 0 | 18 | 0 | restriction endonuclease subunit S |
| YP\_500448.1 | SACOL\_RS09615 | 0 | 18 | 0 | S8 family serine peptidase |
| YP\_500870.1 | SACOL\_RS11210 | 0 | 18 | 0 | SAP domain-containing protein |
| YP\_498762.1 | SACOL\_RS00930 | 0 | 18 | 0 | sce7725 family protein |
| YP\_500432.1 | SACOL\_RS09535 | 0 | 16 | 0 | SMEK domain-containing protein |
| YP\_498658.1 | SACOL\_RS00410 | 0 | 18 | 0 | tandem-type lipoprotein |
| YP\_498647.1 | SAS\_RS00305 | 0 | 18 | 0 | TfoX/Sxy family protein |
| WP\_000142039.1 | SACOL\_RS01465 | 0 | 18 | 0 | TIGR01741 family protein |
| YP\_498862.1 | SACOL\_RS01430 | 0 | 17 | 0 | TIGR01741 family protein |
| WP\_000142145.1 | SACOL\_RS01480 | 0 | 15 | 0 | TIGR01741 family protein |
| WP\_015581778.1 | SACOL\_RS01475 | 0 | 15 | 0 | TIGR01741 family protein |
| YP\_498866.1 | SACOL\_RS01485 | 0 | 15 | 0 | TIGR01741 family protein |
| WP\_000251965.1 | SACOL\_RS09520 | 0 | 18 | 0 | transposase |
| WP\_001790863.1 | SACOL\_RS15110 | 0 | 18 | 0 | transposase |
| WP\_006191819.1 | SACOL\_RS02100 | 0 | 18 | 0 | twin-arginine translocase subunit TatC |
| WP\_000791729.1 | SACOL\_RS04400 | 0 | 18 | 0 | von Willebrand factor binding protein Vwb |
| WP\_002470719.1 | SAUSA300\_RS00280 | 0 | 15 | 0 | zinc-binding dehydrogenase |

**Supplemental Data 11.** Clinical characteristics of subjects infected with MRSA belonging to distinct clusters by whole genome sequencing.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Characteristic** | **Cluster A****N = 54** | **Cluster B****N = 14** | **Cluster C****N = 6** | ***P******overall*** | ***P******A vs B*** |
| **Age**, years† Median [IQR] | 24.1[14.8 - 32.5] | 11.1[8.5 - 17.2] | 19.1[5.2 – 29.0] | 0.005 \* | 0.0009 # |
| **MRSA acquisition date, Median [IQR]** | 3/31/11[3/12/07 – 9/16/14] | 8/11/13[1/13/11– 7/22/15] | 11/27/14[5/17/06 – 4/17/17] | 0.0547 \* | 0.0203 # |
| **Female Sex** | 28 (51.9%) | 6 (42.9%) | 2 (33.3%) | 0.69 ‡ | 0.77 ‡ |
| **Genotype** |  |  |  | 0.62 ‡ | 0.43 ‡ |
| ∆F508/∆F508  | 29 (53.7%) | 6 (42.9%) | 2 (33.3%) |  |  |
| ∆F508/other  | 22 (40.7%) | 8 (57.1%) | 4 (66.7%) |  |  |
| Other/other | 3 (5.6%) | 0 | 0 |  |  |
| **CFTR related metabolic syndrome** | 0 | 1 (7.1%) | 0 | - | - |
| **Lung Transplant as of 1 Jan 2017** | 4 (7.4%) | 0 | 0 | - | - |
| **Outcome\*\*** | **Cluster A****N = 50** | **Cluster B****N = 13** | **Cluster C****N = 6** | ***P******overall*** | ***P******A vs B*** |
| **Sputum production**N (%) | 45 (90%) | 11 (84.6%) | 5 (83.3%) | 0.5482‡ | 0.6266 ‡ |
| ***P. aeruginosa***N (%) | 37 (74%) | 7 (54.0%) | 5 (83.3%) | 0.3711 ‡ | 0.1857 ‡ |
| **Spirometry performed** N (%) | 47 (94.0%) | 13 (100%) | 5 (83.3%) | 0.4389 ‡ | 1.00 ‡ |
| **FEV1** % PredictedMedian [IQR] | 64.0 [53 – 88] | 98.0[86.0 – 116.0] | 67.0 [45.0 – 78.0] | 0.001 \* | 0.0003 # |

† Age determined on July 1, 2017. \*\*Outcome data from calendar year 2017, excluding measurements after lung transplant and subjects with CFTR related metabolic syndrome. *P* values determined by ‡Fisher’s exact test, \*Kruskal-Wallis test, or # Wilcoxon rank sum test.

**Supplemental Methods:**

We selected a pangenomic reference derived from 25 genomes selected by Chaves-Moreno et al. PloS one. 2015;10(12):e0145861. These included COL, Ed98, JH1, JH9, MRSA252, MSSA476, Mu3, Mu50, MW2, N315, NCTC8325, Newman, Rf122, USA FPR3757, USA TCH1516, 04-02981, 71193, ECTR2, Ed133, JKD6008, LGA251, M013, MSHR1132, ST398, and VC40. These 25 genomes included 65,322 genes. We downloaded Genbank files for each strain. We exported the FASTA file containing each gene’s nucleotide sequence and aligned these to genome assemblies of our *S. aureus* clinical isolates using HISAT2. We produced a table with 65,322 rows for each gene and 97 columns for each strain, with 1 indicating detection of sequence alignment and 0 indicating no sequence alignment.

Many of the genes in our complete genome set are orthologous but have allelic sequence variations between reference strains. To reduce redundancy, we combined genes having identical Genbank inference tag numbers. This reduced the number of rows from 65,322 to 4,918 based on the number of unique Genbank inference tags. If at least one allele of a given inference tag was detected, we considered the gene to be present.

Of the 4,918 genes in our reference, 866 genes were not detected. 2,427 genes were detected in all 97 isolates. We used the 1,625 genes that were detected at least once but not in every isolate as our accessory genome to determine clusters of *S. aureus* based on genome content. We used a K-means approach to group the isolates into three different clusters. We compared the prevalence of accessory genes in the three clusters.