# Expansion of Invasive Group A *Streptococcus* M1$_{UK}$ Lineage in Active Bacterial Core Surveillance, United States, 2019–2021

Yuan Li, Joy Rivers, Saundra Mathis, Zhongya Li, Sopio Chochua, Benjamin J. Metcalf, Bernard Beall, Jennifer Onukwube, Christopher J. Gregory, Lesley McGee

From 2015–2018 to 2019–2021, hypertoxigenic M1$_{UK}$ lineage among invasive group A *Streptococcus* increased in the United States (1.7%, 21/1,230 to 11%, 65/603; p<0.001). M1$_{UK}$ was observed in 9 of 10 states, concentrated in Georgia (n = 41), Tennessee (n = 13), and New York (n = 13). Genomic cluster analysis indicated recent expansions.

The M1$_{UK}$ lineage of group A *Streptococcus* (GAS) is a hypertoxigenic clone within the serotype M1 GAS strain and has been associated with increased scarlet fever and invasive GAS (iGAS) disease incidence in the United Kingdom since 2014 (*1–3*). M1$_{UK}$ carries 27 characteristic lineage-defining single-nucleotide variants (SNVs) that distinguish it from other globally circulating M1 GAS clones (*1*). By 2020, M1$_{UK}$ had also became the dominant clone among M1 GAS in England (*3*), the Netherlands (*4*), and Australia (*5*) and showed substantial presence in Canada (*6*).

In the United States, M1$_{UK}$ was identified as a minor clone of M1 iGAS isolates in the Active Bacterial Core surveillance (ABCs) system, a laboratory- and population-based surveillance system for invasive bacterial infections that is currently implemented in 10 US states (*7*), in 2015–2018 (*8*). Using genomic surveillance data in ABCs, we investigated the trend of M1$_{UK}$ in 2019–2021 and documented the characteristics of iGAS infections caused by M1$_{UK}$.

## The Study

We identified iGAS cases through ABCs and mapped whole-genome sequencing reads of M1 isolates against the M1 reference genome MGAS5005 to identify M1UK based on previously reported characteristic M1UK SNVs (*1*). We constructed phylogenetic trees by using kSNP3.0 software (*9*). We identified genomic clusters by using a hierarchical cluster analysis with a cutoff value of 10 SNVs as described (*10*). We evaluated change of M1UK proportion among M1 iGAS over time by using the $\chi^2$ test for trend in proportions (trend test). We used the Fisher exact test to assess equality of proportions. All p values were 2 sided, and we considered p<0.05 statistically significant. We performed all analyses by using R software version 3.4.3 (The R Foundation for Statistical Computing, https://www.r-project.org).

We submitted all whole-genome sequencing data files of the study isolates to the National Center for Biotechnology Information Sequence Read Archive (BioProject no. PRJNA395240). Accession numbers of the 86 M1$_{UK}$ isolates are provided (Appendix Table 4, https://wwwnc.cdc.gov/EID/article/29/10/23-0675-App1.pdf).

During 2019–2021, a total of 603 cases of M1 iGAS infections were documented through ABCs. Among those cases, 65 (11%) were caused by the M1$_{UK}$ clone (Figure 1, panel A), and the percentage was significantly higher than that observed during 2015–2018 (1.7%, 21/1,230; p<0.001). The trend test indicated a significant increasing trend in the M1$_{UK}$ proportion among M1 iGAS isolates during 2015–2021 (p<0.001). During 2015–2021, most M1$_{UK}$ cases (67/86) were concentrated in 3 states: Georgia (41 cases,) Tennessee (13 cases), and New York (13 cases), although the M1$_{UK}$ clone was found in 9 of the 10 ABCs sites (Figure 1, panel B). Nearly one third of all M1$_{UK}$ infections (28/86) occurred in the first quarter of 2020 (Figure 1, panel B). During 2015–2021, a total of 12 iGAS isolates

were identified as the intermediate lineages, containing 13 (n = 4) or 23 (n = 8) of the 27 characteristic M1$_{UK}$ SNVs (Appendix Figure 1), and they did not show significant expansion from 2015–2018 through 2019–2021 (p = 0.07).

Phylogenetic analysis of the 86 M1$_{UK}$ isolates showed 9 distinctive genomic clusters (Figure 2). Each genomic cluster contained 2–21 genomically closely related isolates, and collectively those clusters accounted for 74 (86%) of all M1$_{UK}$ isolates (Figure 2). For 2 M1$_{UK}$ isolates within a same cluster, the median pairwise genomic distance was 3 SNVs (interquartile range [IQR] 1.5–6), consistent with continued transmission from a recent introduction event. However, for 2 M1$_{UK}$ isolates not in the same cluster, the median pairwise genomic distance was 33 SNVs (IQR 28–38), indicating some degree of genomic diversity within M1$_{UK}$, although not as much as the diversity observed among 100 randomly selected globally circulating M1 GAS clone isolates in ABCs, 2015–2021 (median 63 SNVs, IQR 49–115). (Appendix Figure 1).

The clusters displayed clear signatures of temporal and geographic relatedness (Appendix Figure 2). For example, the largest cluster, cluster_1, showed a sharp increase of cases at the beginning of 2020, followed by a rapid decrease. The second largest cluster, cluster 2, showed relatively stable case numbers spanning from the third quarter of 2018 to the third quarter of 2020. Within a genomic cluster, most M1$_{UK}$ iGAS were identified in 1 or 2 states, suggesting a localized spread of the infection.

Overall, M1$_{UK}$ and non-M1$_{UK}$ M1 isolates had many common genetic features of the contemporary M1 *S. pyogenes* strain (Table). The M1$_{UK}$ clone had a higher proportion of isolates that had the streptococcal pyrogenic exotoxin gene *speC* (4.7% [4/86] vs. 1.4% [24/1,747]; p = 0.039), the super antigen A gene *ssa* (2.3% [2/86] vs. 0.1% [2/1,747]; p = 0.012), and the extracellular streptodornase D gene *sda1* (also known as *sdaD2*; 100% [86/86] vs. 92% [1,613/1,747]; p = 0.002). The *speC* and *ssa* genes were found in 4 nonclustered M1$_{UK}$ isolates, of which 2 isolates had both genes, suggesting acquisition of prophage ΦHKU488.vir (*5*).

Patients infected by the M1$_{UK}$ strain showed similar age, sex, and syndrome distribution compared with patients infected by non-M1$_{UK}$ M1 GAS (Table), except that M1$_{UK}$ isolates were more likely to be found in patients with pneumonia (33% vs. 22%; p = 0.033). The case-fatality rate was high for M1$_{UK}$ iGAS infection (22%) although it was not significantly different from that of non-M1$_{UK}$ M1 iGAS (15%; p = 0.089). In subgroup analysis stratified by time (2015–2018,
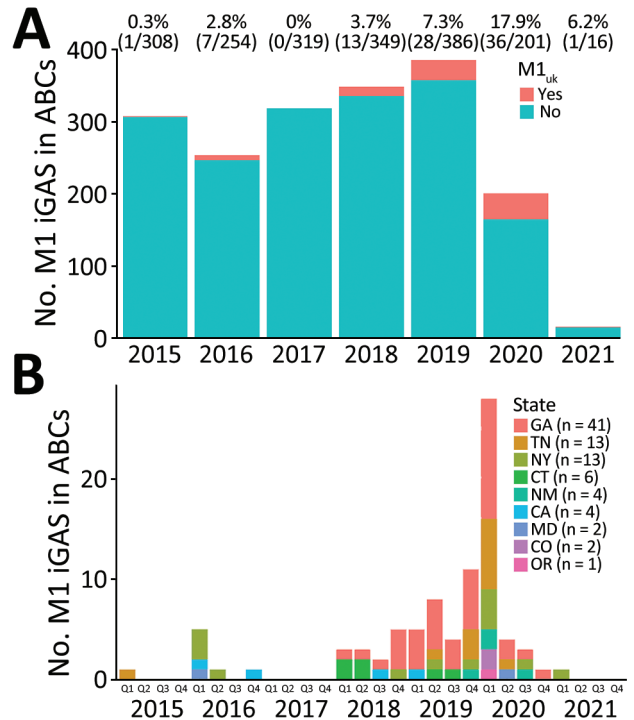


**Figure 1.** Expansion of M1$_{UK}$ lineage in serotype M1 iGAS in the United States, 2015–2021. A) Counts and percentages of M1$_{UK}$ isolates among M1 iGAS isolates in ABCs during 2015–2021. B) Number of M1$_{UK}$ infections over time in 9 states that are part of the ABCs system. Key shows total number of M1$_{UK}$ infections during 2015–2021 for each state. ABCs, Active Bacterial Core Surveillance System; iGAS, invasive group A *Streptococcus* disease; Q, quarter.

2019–2021) and location (GA, TN, and NY only), M1$_{UK}$ isolates were associated with higher proportions of *speC*, *ssa*, *sda1*, and pneumonia compared with non-M1$_{UK}$ isolates in all 3 subgroups (Appendix Tables 1–3), except for *speC* in 2019–2021. The difference in subgroup analysis was generally not statistically significant, potentially caused by smaller sample size and reduced power in a subgroup.

## Conclusions

This study demonstrates a substantial increase of M1$_{UK}$ lineage during 2019–2021 in the ABCs sites in the United States. Additional data are needed to determine variance in M1$_{UK}$ iGAS incidence across states outside the 10 states in ABCs. The proportion of M1$_{UK}$ iGAS in ABCs remains much lower than that reported in England (*3*), Australia (*5*), and the Netherlands (*4*). We documented the mode of expansion for the M1$_{UK}$ lineage in the United States by determining whether the 86 M1$_{UK}$ iGAS cases could be explained by 1 recent introduction or multiple ones. We tracked the shape and characteristics of epidemiologic curves for each

cluster, which could help understand different patterns of disease transmission. The increase was associated with the formation and expansion of multiple genomic clusters in which each cluster was mostly found in only 1 or 2 states. The results suggested that the M1$_{UK}$ clone might have been introduced and
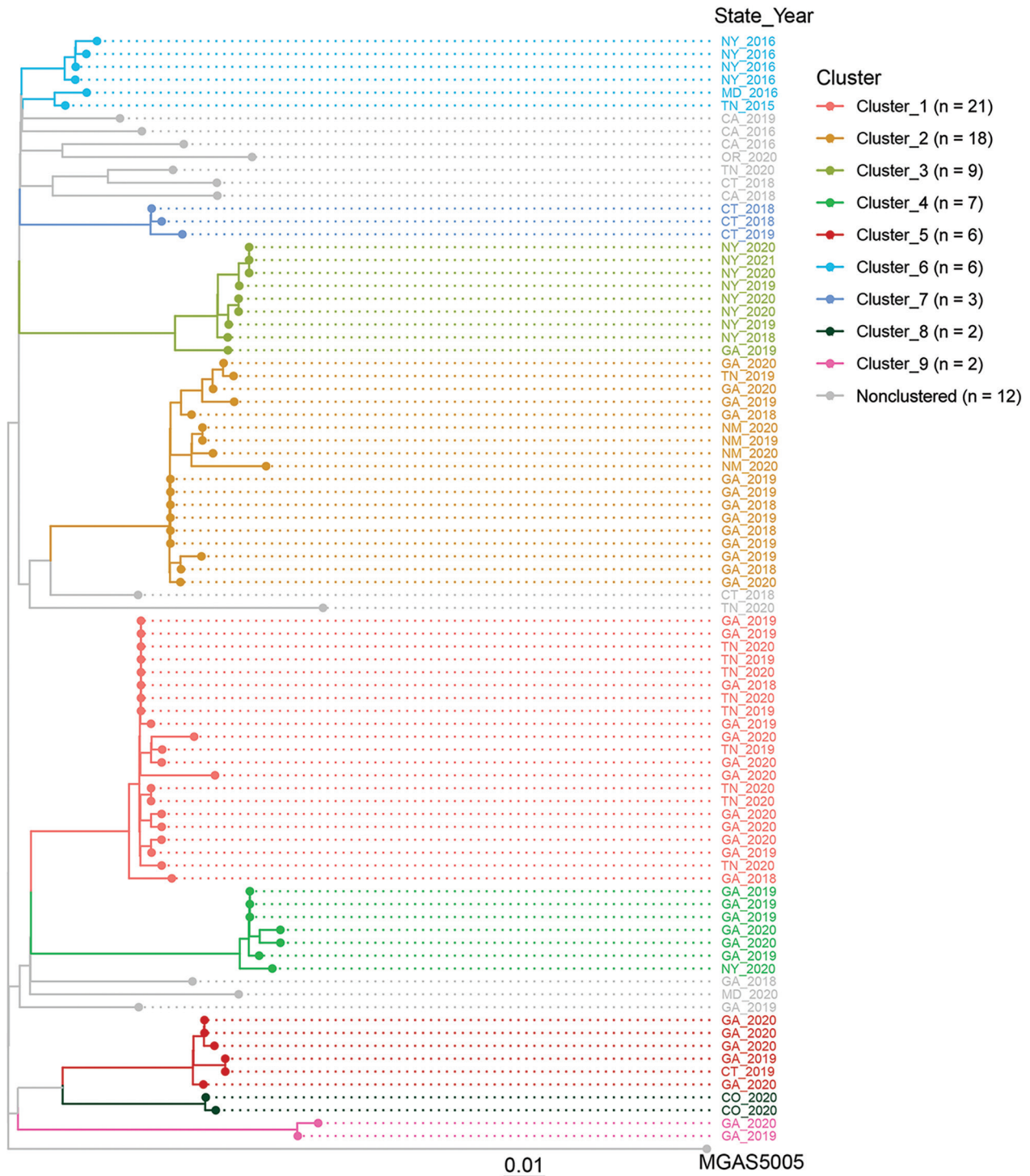


**Figure 2.** Genomic clusters of M1$_{UK}$ invasive group A *Streptococcus* disease, United States, 2015–2021. Core-genome phylogenetic tree of 86 M1$_{UK}$ invasive group A *Streptococcus* disease isolates and the reference M1 genome MGAS5005 was based on 462 core single-nucleotide variant sites generated by kSNP3.0 software (*9*). Tip colors indicate 9 groups of genomically closely related isolates (genomic clusters). Key shows total number of M1$_{UK}$ isolates in each cluster. Scale bar indicates expected nucleotide substitutions per site.

**Table.** Strain and patient features of M1$_{UK}$ iGAS compared with other M1 iGAS in ABCs, United States, 2015–2021

| Characteristic | M1 iGAS, no. (%) cases | | p value† |
| --- | --- | --- | --- |
| | M1$_{UK}$, n = 86 | Non-M1$_{UK}$, n = 1,747 | |
| Strain feature‡ | | | |
| Antimicrobial susceptibility | | | |
| Penicillin nonsusceptible | 0 | 0 | 1.000 |
| Erythromycin nonsusceptible | 0 | 21 (1.2) | 0.621 |
| Clindamycin nonsusceptible | 0 | 20 (1.1) | 1.000 |
| Tetracycline nonsusceptible | 0 | 18 (1) | 1.000 |
| Levofloxacin nonsusceptible | 0 | 9 (0.5) | 1.000 |
| Pyrogenic exotoxin genes | | | |
| *speA* | 86 (100) | 1,720 (98.5) | 0.635 |
| *speC* | 4 (4.7) | 24 (1.4) | 0.039 |
| *speG* | 86 (100) | 1747 (100) | 1.000 |
| *speH* | 0 | 1 (0.1) | 1.000 |
| *speI* | 0 | 1 (0.1) | 1.000 |
| *speJ* | 86 (100) | 1,747 (100) | 1.000 |
| *speK* | 0 | 2 (0.1) | 1.000 |
| *speL* | 0 | 0 | 1.000 |
| *speM* | 0 | 0 | 1.000 |
| *Ssa* | 2 (2.3) | 2 (0.1) | 0.012 |
| *smeZ* | 85 (98.8) | 1,737 (99.4) | 0.411 |
| Other virulence factors | | | |
| *hasA* hyaluronic acid synthetase, capsule | 86 (100) | 1,03 (97.5) | 0.266 |
| Virulence-associated DNase, SDA1§ | 86 (100) | 1,613 (92.3) | 0.002 |
| Patient characteristic | | | |
| Age, y | | | |
| <18 | 12 (14) | 233 (13.3) | 0.871 |
| 18–34 | 5 (5.8) | 178 (10.2) | 0.266 |
| 35–49 | 19 (22.1) | 333 (19.1) | 0.484 |
| 50–64 | 21 (24.4) | 445 (25.5) | 0.899 |
| 65–74 | 15 (17.4) | 289 (16.5) | 0.768 |
| ≥75 | 14 (16.3) | 269 (15.4) | 0.762 |
| Sex | | | |
| M | 41 (47.7) | 955 (54.7) | 0.223 |
| F | 45 (52.3) | 792 (45.3) | 0.223 |
| Clinical syndrome | | | |
| Cellulitis | 25 (29.1) | 633 (36.2) | 0.205 |
| Bacteremia without focus | 11 (12.8) | 276 (15.8) | 0.544 |
| Pneumonia | 28 (32.6) | 384 (22.0) | 0.033 |
| Necrotizing fasciitis | 5 (5.8) | 147 (8.4) | 0.546 |
| Streptococcal toxic shock syndrome | 7 (8.1) | 95 (5.4) | 0.328 |
| Death | 19 (22.1) | 260 (14.9) | 0.089 |

*ABCs, Active Bacterial Core Surveillance System; iGAS, invasive group A *Streptococcus* disease.
†By Fisher exact test.
‡All strain features, including antimicrobial susceptibility, pyrogenic exotoxin genes, and other virulence factors, were inferred from whole-genome sequencing data.
§Detecting genetic marker for the *sda1* gene (GenBank accession no. AY452036.1), which is identical to the *sdaD2* gene (M5005_Spy1415; GenBank accession no. AAZ52033.1).

circulated in different geographic locations in the United States, rather than spreading from a recent single introduction event.

In 2020, *emm*1 was the leading cause of iGAS only in Georgia and New York in ABCs. In that year, the proportion of M1$_{UK}$ isolates among *emm1* iGAS was 38% (16/42) in Georgia and 25% (5/20) in New York. It appeared that M1$_{UK}$ lineage followed the same state preferences as M1 in general. In recent years, there were rapidly expanding clusters of *emm* types that were not historically so prevalent within several different states, mostly pattern E lineages (*emm*11,49,82,92,60) and pattern D lineages (*emm*83,59,81), which was associated with increasing proportions of disadvantaged persons and led to drastic changes in *emm* type distributions in those states (*11,12*).

Although the *speC* and *ssa* genes were associated with M1$_{UK}$ isolates, they were present in <5% of these isolates, and the biologic role of this association is unclear. It is crucial to monitor the spread of this variant and the associated virulence determinants to inform development of effective prevention and treatment strategies.

This study used the *Streptococcus pyogenes* multilocus sequence typing website (https://pubmlst.org/organisms/streptococcus-pyogenes) hosted at the University of Oxford.

## About the Author

Dr. Yuan Li is a microbiologist and bioinformatician in the National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA. His primary research interests are integration of laboratory and epidemiologic data to inform disease surveillance, outbreak responses, and vaccine strategies.

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Address for correspondence: Yuan Li, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mailstop H18-1, Atlanta, GA 30329-4027, USA; email: yqh8@cdc.gov