Supplemental Material

Supplemental Materials and Methods

Bacterial strains and growth conditions. The strains used in this study are listed in Table S1 (Supplemental Material). MGAS10870 is a serotype M3 GAS strain isolated in 2002 from an individual with a soft tissue infection in Ontario, CA (1). The genome of strain MGAS10870 has been sequenced (1). MGAS23412 was isolated from an individual with GAS pharyngitis and MGAS23431 was isolated from the same individual 63 days later during asymptomatic carriage (2). The genomes of MGAS23412 and MGAS23431 have been sequenced (3). GAS strains were grown on trypticase soy agar containing 5% sheep blood (SBA) (Becton-Dickinson), in Todd-Hewitt broth containing 0.2% (wt/vol) yeast extract (THY) (Difco Laboratories), or on THY agar. All strains were grown at 37°C supplemented with 5% CO_2 unless otherwise indicated. When needed, media were supplemented with chloramphenicol (Sigma-Aldrich) at 10 µg/mL or spectinomycin (Sigma-Aldrich) at 150 µg/mL. Cloning experiments used *E. coli* DH5α or TOP10 (Invitrogen) grown in Luria-Bertani (LB) broth or on LB agar (Difco Laboratories) supplemented with ampicillin (Sigma-Aldrich) at 100 µg/mL or chloramphenicol 20 µg/mL when appropriate.

Generation of isoallelic mutants in MGAS10870 and MGAS23431. Plasmids and primers used in this study are listed in Table S2 (Supplemental Material). We used a previously described procedure for generating the mutant MGAS10870*liaS*^{R135G} (3, 4). Briefly, the *liaS*^{R135G} allele from MGAS23431 (carrier strain) was amplified with primer pair 2307R and 2306F and subsequently ligated into the *E. coli*-Gram positive shuttle

vector pJL1055 (5, 6) using *Bam*HI and *Xho*I to generate pJSF38. Electrocompetent cells of MGAS10870 were transformed with pJSF38 and allelic replacement carried out as previously described (4, 5). Likewise, the mutant MGAS23431*liaS*^{WT} was generated using the same primers to amplify *liaS*^{WT} from MGAS10870 and ligated into pJL1055 using the same restriction enzymes to generate pJSF39. Electrocompetent cells of MGAS23431 were transformed with pJSF39 and allelic replacement carried out as previously described (3, 4). All mutants were confirmed using Sanger sequencing (Applied Biosystems).

Cultured human epithelial cell adherence assays. Adherence to cultured human epithelial cells was carried out as previously described (3). HaCaT cells were seeded at a density of 6 x 10^5 in 2 mL high glucose DMEM with L-glutamine and 10% FBS in a 12-well plate. Cells were incubated overnight at 38.5°C. The appropriate GAS strains were grown to mid-exponential phase (OD_{600} ≈ 0.5) in THY, pelleted, washed once with sterile PBS, and suspended in an equal volume PBS. Approximately 1 x 10^7 CFU GAS (MOI ≈ 10) were added to 8 replicate wells, rocked briefly, and incubated for 2 hours at 37°C. Wells were subsequently washed with PBS (2 x 1 mL, 2 x 2 mL) and incubated at 37°C with 1 mL PBS containing 1% saponin (Oxoid). Cells were released from wells by pipetting, serially diluted, and plated on SBA to enumerate GAS. Percent adherence was calculated by dividing recovered CFU by the original inoculum.

***Ex vivo* bactericidal assays in human blood**. Growth in whole human blood was conducted under a Houston Methodist Research Institute Institutional Review Board

47 experimental protocol and performed as described by Lancefield (8). A minimum of two,
48 healthy, non-immune adult donors were used for each experiment. Bacteria were grown
49 to mid-exponential phase (OD_{600} ≈ 0.5) in THY, pelleted, and suspended in an equal
50 volume of phosphate-buffered saline (PBS). Approximately 100 CFU of each GAS strain
51 was used to inoculate 300 µl of fresh human blood in quadruplicate. Samples were
52 incubated at 37°C with 5% CO_2 with gentle rotation for 3 hours, serially diluted in PBS,
53 and subsequently plated on SBA. Multiplication factors were calculated by dividing the
54 number of CFU/mL after 3 h incubation by the initial inoculum.
55
56 **RNA isolation and quantitative real-time PCR analysis**. GAS strains were grown
57 overnight THY, diluted 1:50 in fresh THY, and incubated. Samples were taken at
58 defined time points for determination of OD_{600} and RNA isolation. RNA was isolated and
59 purified with an RNeasy Mini Kit (Qiagen) as previously described (4). Quantity and
60 quality of RNA was determined using an Agilent 2100 Bioanalyzer and RNA 6000 Nano
61 Kit (Agilent Technologies).
62 TaqMan (Life Technologies) quantitative real-time PCR (qRT-PCR) on cDNA
63 produced using SuperScript III (Invitrogen) was performed with an ABI7500 Fast Real-
64 Time system. TaqMan primers and probes used in analyses are listed in Table S2
65 (Supplemental Material). The endogenous control gene *tufA* was used for all TaqMan
66 analyses. Transcript levels were compared between strains using the $\Delta\Delta C_T$ method
67 (user bulletin no. 2, ABI Prism 7700 Sequence Detection System; Life Technologies).
68 All reactions were performed in triplicate using RNA purified from at least three biologic
69 replicates.

Supplemental References

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Supplemental Figures

Figure S1.

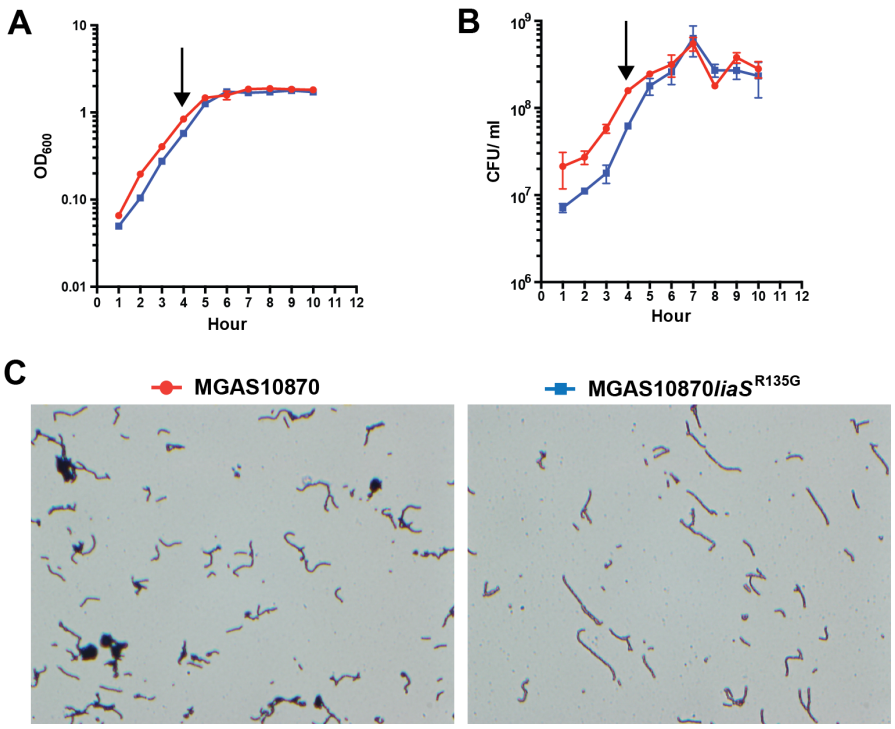

Figure S1. Strain lacking LiaS has altered growth *in vitro*. Growth curve as measured by optical density at 600 nm (OD_{600}) (**A**) or colony forming units (CFU) (**B**) in a rich medium (THY) for MGAS10870 (wild-type, red) and MGAS10870*liaS*^{R135G} (carrier, blue). Black arrow indicates time point at which samples were taken for Gram's stain and microscopy. Error bars represent standard error of the mean. (**C**) Gram's stain and light microscopy of strains during growth in A and B. Original magnification 400x.

Supplemental Tables

Table S1. Strains used in this study.

Strain	Description	Reference
MGAS10870	Wild-type invasive serotype M3 GAS strain.	(1)
MGAS10870*liaS*^{R135G}	Isoallelic mutant of MGAS10870 in which the carrier *liaS*^{R135G} replaced the *liaS*^{WT} allele	This study
MGAS23412	Serotype M3 GAS pharyngitis strain isolated at Day 0	(3)
MGAS23431	Serotype M3 GAS carrier strain isolated at Day 63 from same patient as MGAS23412	(3)
MGAS23431*liaS*^{WT}	Isoallelic mutant of MGAS23431 in which *liaS*^{R135G} was replaced with *liaS*^{WT}	This study

Table S2. Plasmids and primers used in this study.

Plasmid	**Description**	**Reference/Source**
pCR2.1	General purpose cloning vector	Invitrogen
pJL1055	Temperature sensitive *E. coli*/GAS shuttle vector	D. Kasper
pJSF38	pJL1055 containing the *liaS*^{R135G} allele from MGAS23431	This study
pJSF39	pJL1055 containing the *liaS*^{WT} allele from MGAS10870	This study
Primer	**Sequence (5'-3')**	**Use**
2305F	TCTTGTGGAACACCGTACCG	PCR

2306F	AAATTTCAGCCGCACTCGAT	PCR
2307R	CTTTAGATGTTAGTTCCATA	PCR
2309R	TAGTTATGCAGATGCAGTCA	PCR
MSP191	GCCTCAACACCGCCTAACTCTGG	*liaR* TaqMan
MSP192	6FAM-TCTGGCTTCAAAGCCAATGCCA-BHQ1	*liaR* TaqMan
MSP193	GGCCTCTAATGGACGTGAAGGGG	*liaR* TaqMan
MSP194	ACTTCAATTCGACTAGCTTTAGCA	*liaS* TaqMan
MSP195	6FAM-ACGTGTTGCTAATGAATTCTTGGGCA-BHQ1	*liaS* TaqMan
MSP196	GGAAACCATTGCTCAGCTTCC	*liaS* TaqMan
MSP197	AGGGATTGGTTATCCGTTTCTTT	*liaF* TaqMan
MSP198	6FAM-CGTTGCGCAAATCATATTGCTGACA-BHQ1	*liaF* TaqMan
MSP199	TCCATATACGGAAGCGTTGATTT	*liaF* TaqMan

Table S3. Differentially expressed genes in MGAS10870*liaS*^{R135G} compared to MGAS10870 in mid-exponential phase growth.

Locus tag[1]	Gene Name	Fold-change	*P*-value[2]
SpyM3_0029	-	1.8	8.9E-03
SpyM3_0036	*adh2*	-2.0	1.1E-03
SpyM3_0037	*adh1*	2.0	6.3E-04
SpyM3_0068	-	4.7	4.4E-23
SpyM3_0077	-	3.0	4.8E-11
SpyM3_0089	*pepA*	2.1	8.9E-05

SpyM3_0105	-	-2.0	5.7E-05
SpyM3_0123	-	-1.8	1.7E-02
SpyM3_0124	-	-1.8	2.1E-03
SpyM3_0132	-	-2.0	1.4E-04
SpyM3_0133	*metB*	2.2	1.1E-02
SpyM3_0152	-	-1.8	1.6E-03
SpyM3_0160	*hasC.2*	-2.3	6.2E-09
SpyM3_0161	*gpsA*	-1.9	9.7E-05
SpyM3_0235	*atmE*	1.9	1.6E-02
SpyM3_0243	-	1.9	1.6E-04
SpyM3_0305	-	2.2	2.0E-06
SpyM3_0306	-	-1.9	1.8E-04
SpyM3_0307	-	1.9	1.9E-04
SpyM3_0334	-	-1.9	1.0E-02
SpyM3_0346	*mutR*	2.1	2.5E-02
SpyM3_0359	*gloA*	-1.7	3.4E-02
SpyM3_0361	*pepQ*	-1.7	3.4E-02
SpyM3_0363	-	-2.4	8.3E-10
SpyM3_0364	-	-2.5	5.6E-11
SpyM3_0406	-	-2.3	5.7E-06
SpyM3_0407	-	-2.3	1.1E-05
SpyM3_0411	-	-3.3	<1.0E-23
SpyM3_0428	-	-1.8	2.2E-03

SpyM3_0429	*pepF*	-1.9	2.8E-04
SpyM3_0438	-	-1.8	1.2E-02
SpyM3_0489	-	1.9	8.9E-03
SpyM3_0514	*rexA*	-1.8	4.0E-03
SpyM3_0534	-	1.8	4.7E-03
SpyM3_0535	-	2.7	5.0E-12
SpyM3_0536	-	1.9	2.7E-04
SpyM3_0541	-	-1.7	4.0E-02
SpyM3_0547	*folC.2*	-2.0	3.3E-04
SpyM3_0548	-	-1.9	5.3E-04
SpyM3_0575	-	1.7	4.5E-02
SpyM3_0581	-	-2.2	1.8E-05
SpyM3_0630	-	2.1	1.5E-06
SpyM3_0655	-	1.9	1.9E-03
SpyM3_0656	-	1.8	5.6E-03
SpyM3_0821	*gid*	2.2	2.7E-05
SpyM3_0837	*citC*	-2.1	2.5E-06
SpyM3_0838	-	-2.2	8.8E-08
SpyM3_0853	*fhs.1*	2.4	2.0E-06
SpyM3_0871	*coaA*	-2.2	1.7E-04
SpyM3_0896	-	1.8	1.8E-03
SpyM3_0897	-	2.0	1.6E-05
SpyM3_0899	-	1.7	2.6E-02

SpyM3_0918	-	-1.7	3.6E-02
SpyM3_0991	*dltD*	-1.8	1.5E-03
SpyM3_0992	*dltC*	-1.8	2.1E-03
SpyM3_0993	*dltB*	-2.6	1.0E-11
SpyM3_0994	*dltA*	-2.0	3.1E-05
SpyM3_0995	-	-1.8	2.0E-03
SpyM3_1048	*nrdH*	-1.9	7.3E-05
SpyM3_1049	*nrdE.1*	-1.9	2.8E-04
SpyM3_1050	*nrdF*	-1.9	2.5E-04
SpyM3_1057	-	1.8	3.4E-02
SpyM3_1160	-	2.0	1.0E-03
SpyM3_1173	*ftsA*	2.0	4.8E-06
SpyM3_1180	*glcK*	1.9	8.6E-04
SpyM3_1181	-	1.9	1.5E-04
SpyM3_1268	-	-2.0	1.1E-04
SpyM3_1269	*ccdA*	-2.1	2.7E-06
SpyM3_1270	-	-1.8	4.5E-03
SpyM3_1272	-	-2.0	7.4E-05
SpyM3_1299	-	2.1	2.9E-02
SpyM3_1363	*cysM*	1.7	7.6E-03
SpyM3_1409	*sdn*	2.7	2.8E-12
SpyM3_1459	-	-2.1	1.5E-05
SpyM3_1475	*nagA*	2.5	2.2E-06

SpyM3_1504	*hit*	-1.8	9.6E-04
SpyM3_1505	-	-1.8	8.6E-04
SpyM3_1517	*accA*	2.0	6.7E-06
SpyM3_1518	*accD*	1.8	3.1E-03
SpyM3_1525	*fabK*	1.7	2.2E-02
SpyM3_1527	*fabH*	2.2	1.9E-08
SpyM3_1528	-	1.7	9.9E-03
SpyM3_1537	-	2.4	6.6E-06
SpyM3_1566	*pmi*	-2.1	2.2E-05
SpyM3_1591	-	-1.8	2.3E-03
SpyM3_1601	*norA*	2.7	4.6E-04
SpyM3_1614	-	-1.9	3.7E-04
SpyM3_1619	-	-1.8	5.3E-03
SpyM3_1657	*lacC.2*	1.7	3.2E-02
SpyM3_1666	-	3.2	1.4E-09
SpyM3_1698	*ska*	-2.4	2.8E-09
SpyM3_1699	-	-1.9	6.4E-03
SpyM3_1712	*pabP*	-2.1	5.9E-04
SpyM3_1713	*trpG*	-2.7	5.8E-09
SpyM3_1714	-	-2.2	1.7E-05
SpyM3_1737	-	1.8	2.0E-03
SpyM3_1738	-	-2.0	5.7E-04
SpyM3_1740	*prsA*	1.6	4.8E-02

SpyM3_1741	-	2.4	8.2E-08
SpyM3_1742	*speB*	2.4	1.1E-08
SpyM3_1745	*mf*	1.7	8.5E-03
SpyM3_1792	-	1.7	1.2E-02
SpyM3_1799	*spxA2*	-5.4	<1.0E-23
SpyM3_1812	-	1.7	4.5E-02
SpyM3_1835	*dnaC*	1.7	2.1E-02
SpyM3_1841	*sdhB*	-2.0	7.2E-06
SpyM3_1842	*sdhA*	-1.9	9.3E-04
SpyM3_1843	-	2.1	1.3E-05
SpyM3_1849	-	-1.7	3.2E-02
SpyM3_1850	-	-1.7	3.5E-02
SpyM3_1857	*guaB*	1.7	2.9E-02

[1] Locus tag as defined in the serotype M3 reference genome MGAS315. Bold font indicates significant differential expression in both growth phases.

[2] *P*-value after Bonferonni correction

Table S4. Differentially expressed genes in MGAS10870*liaS*^{R135G} compared to MGAS10870 in early stationary phase growth.

Locus tag[1]	Gene Name	Fold-change	*P*-value[2]
SpyM3_0011	*hpt*	-1.7	1.0E-02

SpyM3_0012	*ftsH*	-1.6	3.5E-02
SpyM3_0014	-	-2.4	1.1E-08
SpyM3_0034	-	1.7	5.1E-03
SpyM3_0077	-	2.7	6.7E-11
SpyM3_0086	*ackA*	-1.7	3.6E-03
SpyM3_0169	-	1.8	2.5E-05
SpyM3_0187	-	-2.1	1.2E-03
SpyM3_0204	-	2.0	3.4E-05
SpyM3_0231	-	-2.0	5.7E-06
SpyM3_0232	*atmA*	2.0	1.6E-06
SpyM3_0261	-	-1.7	2.8E-02
SpyM3_0321	*cypB*	1.7	1.9E-02
SpyM3_0332	-	1.8	2.2E-04
SpyM3_0363	-	-1.9	1.3E-04
SpyM3_0364	-	-2.0	2.3E-05
SpyM3_0375	*rnc*	-2.3	3.7E-05
SpyM3_0376	*smc*	-2.2	5.5E-06
SpyM3_0411	-	-1.9	3.0E-05
SpyM3_0438	-	-1.9	2.4E-03
SpyM3_0458	-	1.7	1.3E-03
SpyM3_0512	-	2.1	9.7E-06
SpyM3_0514	*rexA*	-1.8	1.5E-03
SpyM3_0515	-	-2.0	3.3E-05

SpyM3_0517	*mscL*	2.4	1.3E-11
SpyM3_0534	-	1.9	1.6E-06
SpyM3_0535	-	2.7	2.0E-15
SpyM3_0536	-	2.3	4.0E-11
SpyM3_0541	-	-1.8	1.2E-03
SpyM3_0546	*gor*	1.8	3.9E-03
SpyM3_0548	-	-2.0	4.6E-06
SpyM3_0551	-	1.6	3.6E-02
SpyM3_0558	*pyrR*	3.3	5.3E-13
SpyM3_0559	*pyrP*	4.3	6.4E-22
SpyM3_0560	*pyrB*	4.6	3.6E-19
SpyM3_0561	*carA*	5.6	1.9E-38
SpyM3_0562	*carB*	6.2	2.7E-29
SpyM3_0570	-	-1.9	9.6E-03
SpyM3_0578	*fruR*	5.4	7.0E-32
SpyM3_0579	*fruK*	5.6	1.5E-34
SpyM3_0580	*fruA*	3.3	4.1E-23
SpyM3_0602	*dyr*	-2.0	5.1E-06
SpyM3_0603	-	-1.8	1.2E-03
SpyM3_0615	-	1.7	6.5E-03
SpyM3_0616	*pyrF*	3.8	9.4E-13
SpyM3_0617	*pyrE*	5.4	5.2E-25
SpyM3_0618	*amiC*	3.6	4.8E-19

SpyM3_0619	-	2.8	1.8E-14
SpyM3_0620	-	2.9	6.1E-15
SpyM3_0657	-	1.8	4.6E-04
SpyM3_0739	*csrA*	1.7	1.0E-02
SpyM3_0785	*ppnK*	-1.9	6.4E-04
SpyM3_0813	-	1.9	1.2E-06
SpyM3_0871	*coaA*	-2.1	2.3E-03
SpyM3_0886	*mreA*	1.8	6.1E-04
SpyM3_0887	*truB*	1.9	1.2E-02
SpyM3_0895	-	2.5	4.1E-14
SpyM3_0896	-	2.3	3.3E-11
SpyM3_0897	-	2.3	8.0E-11
SpyM3_0898	-	2.2	1.6E-10
SpyM3_0899	-	2.7	3.4E-17
SpyM3_0900	-	2.7	2.8E-17
SpyM3_0914	*dnaE*	1.9	1.3E-04
SpyM3_0980	*glgP*	-1.9	7.9E-04
SpyM3_0981	*malQ*	-2.0	3.4E-05
SpyM3_0983	*malE*	-2.0	5.3E-07
SpyM3_0984	*malF*	-2.3	2.0E-08
SpyM3_0985	*malG*	-2.4	1.9E-07
SpyM3_1019	-	-1.9	2.3E-05
SpyM3_1020	-	2.3	1.1E-04

SpyM3_1046	*ptsI*	-1.8	2.1E-04
SpyM3_1047	*ptsH*	-1.6	2.2E-02
SpyM3_1048	*nrdH*	-2.0	3.8E-03
SpyM3_1050	*nrdF*	-1.8	3.0E-02
SpyM3_1152	-	1.7	1.7E-02
SpyM3_1165	-	1.6	2.1E-02
SpyM3_1173	*ftsA*	1.6	2.1E-02
SpyM3_1198	*argR*	-2.1	2.0E-06
SpyM3_1294	*hyl*	1.6	1.3E-02
SpyM3_1295	-	1.7	1.1E-02
SpyM3_1296	-	1.7	7.3E-03
SpyM3_1299	-	1.8	1.5E-02
SpyM3_1355	*recX*	1.8	1.9E-04
SpyM3_1363	*cysM*	2.2	2.4E-08
SpyM3_1469	-	2.0	6.5E-07
SpyM3_1475	*nagA*	2.6	3.6E-12
SpyM3_1490	*copZ*	2.2	2.3E-07
SpyM3_1491	*copA*	2.4	1.0E-10
SpyM3_1492	*copY*	1.8	1.4E-04
SpyM3_1511	*manL*	-1.8	2.9E-03
SpyM3_1514	-	-1.8	3.2E-02
SpyM3_1517	*accA*	1.9	9.7E-05
SpyM3_1530	*dnaJ*	2.1	5.2E-08

SpyM3_1531	*dnaK*	2.1	3.7E-09
SpyM3_1532	*grpE*	2.3	1.8E-11
SpyM3_1533	*hrcA*	2.0	8.5E-08
SpyM3_1538	-	1.7	1.1E-02
SpyM3_1547	-	1.9	2.2E-05
SpyM3_1566	*pmi*	-1.7	3.2E-02
SpyM3_1591	-	-2.1	1.8E-04
SpyM3_1611	*deoC*	2.5	2.1E-12
SpyM3_1612	*nupC*	1.9	1.7E-04
SpyM3_1613	*udp*	2.9	7.3E-17
SpyM3_1619	-	-1.8	8.2E-04
SpyM3_1645	*salR*	-1.6	4.7E-02
SpyM3_1658	*lacB.2*	1.6	2.4E-02
SpyM3_1666	-	2.9	1.4E-02
SpyM3_1694	*pulA*	-1.9	1.4E-03
SpyM3_1696	*msmK*	1.6	3.4E-02
SpyM3_1700	*dtd*	1.9	1.2E-04
SpyM3_1701	*relA*	1.7	1.0E-02
SpyM3_1711	-	2.8	6.0E-15
SpyM3_1718	*dppA*	-1.8	7.4E-03
SpyM3_1723	-	1.7	7.8E-04
SpyM3_1728	*mga*	-1.9	1.1E-04
SpyM3_1734	-	1.8	3.7E-03

SpyM3_1735	-	2.8	9.3E-13
SpyM3_1736	-	2.8	4.0E-12
SpyM3_1737	-	3.5	2.5E-25
SpyM3_1741	-	2.0	8.3E-08
SpyM3_1742	*speB*	1.6	1.1E-02
SpyM3_1743	-	1.6	4.9E-02
SpyM3_1765	*groEL*	1.7	9.3E-04
SpyM3_1766	*groES*	1.8	2.2E-04
SpyM3_1784	*pepO*	-1.7	1.2E-02
SpyM3_1799	*spxA2*	-3.8	<1.0E-38
SpyM3_1843	-	-2.0	8.2E-04

[1] Locus tag as defined in the serotype M3 reference genome MGAS315. Bold font indicates significant differential expression in both growth phases.

[2] *P*-value after Bonferonni correction