

Streptococcus pneumoniae Serotype 12F-CC4846 and Invasive Pneumococcal Disease after Introduction of 13-Valent Pneumococcal Conjugate Vaccine, Japan, 2017

Appendix

Supplementary Methods and Results

We obtained draft genome data of the serotype 12F isolates that were recovered in Japan between 2013 and 2017. We identified the STs, resistance genes, pili and *pbp1a*, *2b* and *2x* sequences based on assembled contigs using BLAST+ v.2.6.0 (1). For MLST, we downloaded reference sequences of each allele from pubMLST (<https://pubmlst.org/>). We then compared the reference sequences to contigs; extracted sequences that were completely identical to the reference sequence throughout the region were adopted as the allelic numbers. With regard to the resistance genes *pili1* and *pili2*, reference sequences were obtained using BLAST analysis in a previous study (2). The reference sequences of all PBPs were obtained from the *S. pneumoniae* G54 reference sequence that was submitted as NC_011072.1 to the GenBank database. PBP types were assigned using a previously published PBP database (2), and the Japanese original types were published elsewhere (3–5). The novel PBP profile identified in Japan is described below.

Recombination site prediction and phylogenetic analysis

We utilized a single-nucleotide polymorphism (SNP)-based approach to create a phylogenetic tree using Gubbins v.2.2.1 (6). After trimming the obtained raw reads using fastp v.0.20.0 (7), the reads were mapped to the *S. pneumoniae* ASP0581 complete sequence (GenBank accession No. NZ_AP019192.2) using the Burrows-Wheeler Aligner (8) because the isolate was closely related to the tested serotype 12F isolates. After the removal of duplicate

reads and indels using the GATK Best Practices workflow (9), consensus sequence FASTA files were created using VCFtools (10). Low-quality mapping reads with the parameters DP>5, MQ>30 and QD>20 were removed using vcffilter. The Gubbins analysis was performed using the standard parameters. The average recombination rate (r/m) was calculated from the data obtained with Gubbins. Ancestral recombination events that occurred once and spread in the cluster via clonal descent were counted once.

For establishment of the *cps* locus-based phylogenetic tree, we mapped the trimmed reads to the serotype 12F *cps* locus reference sequence (GenBank accession No. CR931660.1), and a phylogenetic tree was obtained using RAxML v8.2.10 (11) with the GTRGAMMA DNA substitution model. The node support was assessed using 500 bootstrap replicates. The model decision was based on the ModelTest-NG results.

***Tn916* analysis**

We extracted the sequences of *Tn916*-like ICEs from the assembled contigs using BLAST+. The reference sequence of *Tn916* (GenBank accession No. U09422.1) was used for the extraction. The analyzed sequences were annotated using Prokka v1.13.7 (12) with the standard parameters. The detailed structures of the region were visualized using ACT (13) and assigned their transposon types. In addition, we conducted a phylogenetic analysis using all serotype 12F isolates. The trimmed reads were mapped on the reference *Tn916* sequence, and the alignment was analyzed using RAxML-ng (14) with GTR+G4. The reference sequence of *Tn916* was used for the outgroup. The model decision was based on the ModelTest-NG results, and the node support was assessed using 3000 bootstrap replicates.

Core genome analysis

We annotated the assembled contigs using Prokka with the standard parameters. After the annotation, we searched pan and core genomes using Roary v3.12.0 (15) with the standard parameters. For all serotype 12F-CC4846 isolates, we identified a total of 2346 genes, including 1898 core genes that were shared by more than 99% of the isolates. For the serotype 12F-ST4846 isolates, we identified a total of 2235 isolates, including 1976 core genes.

Within the target clusters, we searched specific genes of the cluster using Scoary v1.6.16 with the standard parameters, and genes that were exclusive found in each cluster with a p value

<0.01 obtained with Fisher's exact tests followed by the Bonferroni correction were defined as specific genes of the cluster.

The gene regions identified to be ST4846- or ST6945-specific were compared with recombination regions in the Gubbins analysis. We identified the gene regions in the *S. pneumoniae* ASP0581 complete sequence by BLAST+ searching using the gene sequences. Then, we compared the regions with the recombination regions predicted by Gubbins.

Bayesian analysis

We estimated the time of the most recent common ancestor (TMRCA) of the ST4846 and ST6945 clades using BEAST v.1.10.4. The input file for the BEAST analysis did not include recombination regions, and SNP alignment files for each isolate were obtained. For examination of the temporal signal of the inputted dataset, we used TempEst (16) to diagnose the regression of the root-to-tip genetic distance against the sampling time. Analysis of the best-fitting root mean square of the heuristic residual showed that the correlation coefficients (R^2) of all serotype 12F isolates, ST4846 clade isolates, and ST6945 isolates were 0.3405, 0.4194 and 5.8502×10^{-2} , respectively. Although the R^2 of the ST6945 isolates was low, we did not remove any sample because we decided that this quality was due to the short sampling period and/or the small number of isolates belonging to the ST6945 clade. The model was selected through comparisons of the marginal likelihood using path sampling and stepping stone-based marginal likelihood estimation for a strict clock and an uncorrelated relaxed clock in a molecular clock model and a constant size and Bayesian Skygrid in a tree prior model. Consequently, we selected a strict-clock model and a Bayesian Skygrid model for the ST4846 clade analysis and strict clock model and a Bayesian Skygrid model for the ST6945 clade analysis. To obtain an effective sample size (ESS) greater than 200 for all factors, we set the MCMC lengths for ST4846 and ST6945 to 2.0×10^8 and 1.0×10^9 , respectively. We specified a general-time-reversible substitution model with site rate heterogeneity modeled across four gamma distributions (GTR+ Γ 4) for all analyses.

We found one major subclade within the ST4846 clade in the maximum clade credibility tree; thus, we performed a phylogeographic analysis of the 45 ST4846 isolates. We specified an asymmetric discrete trait phylogeographic model utilizing a Bayesian stochastic search variable selection (BSSVS) framework (17) as a metric for comparing the geographic signals between

datasets. For computational efficiency, we aggregated the 14 discrete sampling prefectures into six geographical regions (which are usually used in Japan) in the asymmetric model.

Japan original PBP profile

pbp1a

>JP_1a1

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>JP_1a2

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>JP_1a3

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>JP_2x37

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YV

>JP_2x38

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V

>JP_2x39

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>JP_2x40

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>JP_2x41

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>JP_2x45

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>JP_2x46

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QKMATWLDYLRKFKFGVPTRFGLTDEYAGQLPADNIVSIAQSSFGQGISVTQTQMLRAF
TANDGVMLEPKFISAIYDTNNQSVRKSQKEIVGNPVSKEAASTTRNHMILVGTDPLOYGT
MHYTGKPIITVPGQNVAVKSGTAQIADEKNGGYLVGSTNYIFSVVTMNPANPDFILYV

>JP_2x47

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ANDGVMLEPKFISAIYDTNNQSVRKSQKEIVGNPVSKEAASTTRNHMILVGTDPLOYGTM
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>JP_2x48

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TANDGVMLEPKFISAIYDTNNQSVRKSQKEIVGNPVSKEAASTTRNHMILVGTDPLYGT
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>JP_2x58

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LYV

>JP_2x59

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Appendix Table 1. Strain information of the isolates tested in this study

Isolate name	Accession No.	Serotype	Sequence type	Region	PBP profile			MIC ($\mu\text{g/ml}$)*				
					<i>pbp1a</i>	<i>pbp2b</i>	<i>pbp2x</i>	PCG	CTX	MEM	EM	LFX
PC0217	DRR198414	12F	4846	Tokai	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC0786	DRR198415	12F	4846	Kinki	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC0822	DRR198416	12F	4846	Kanto	37	JP14	JP27	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC0827	DRR198417	12F	4846	Kinki	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC0872	DRR198418	12F	4846	Kanto	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC0882	DRR198419	12F	4846	Kanto	37	JP14	JP27	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC0896	DRR198420	12F	4846	Kanto	37	JP14	JP27	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC0974	DRR198421	12F	4846	Tokai	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1034	DRR198422	12F	4846	Kanto	37	JP14	JP23	0.12	0.5	≤ 0.06	>128	1
PC1035	DRR198423	12F	6945	Kinki	37	4	23	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1037	DRR198424	12F	4846	Kyusyu	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1050	DRR198425	12F	6945	Kinki	37	4	23	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1051	DRR198426	12F	4846	Tohoku	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1053	DRR198427	12F	4846	Kinki	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1084	DRR198428	12F	4846	Kanto	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1114	DRR198429	12F	4846	Tohoku	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1150	DRR198430	12F	6945	Tokai	37	4	23	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1182	DRR198431	12F	4846	Tokai	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1185	DRR198432	12F	4846	Kanto	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1198	DRR198433	12F	4846	Tohoku	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1203	DRR198434	12F	4846	Kanto	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1266	DRR198435	12F	4846	Kinki	37	JP14	JP27	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1271	DRR198436	12F	4846	Kanto	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1277	DRR198437	12F	4846	Kanto	37	JP14	JP27	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1278	DRR198438	12F	4846	Tohoku	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1283	DRR198439	12F	4846	Tohoku	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1285	DRR198440	12F	4846	Kinki	37	JP14	JP27	0.12	0.12	≤ 0.06	>128	1
PC1286	DRR198441	12F	4846	Kanto	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1287	DRR198442	12F	4846	Sanin	37	JP14	JP27	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1293	DRR198443	12F	4846	Sanin	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1296	DRR198444	12F	4846	Tokai	37	JP14	JP27	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1305	DRR198445	12F	4846	Tokai	37	JP14	JP27	0.12	0.12	≤ 0.06	>128	1
PC1314	DRR198446	12F	4846	Tokai	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	0.5
PC1347	DRR198447	12F	4846	Tokai	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1350	DRR198448	12F	4846	Kanto	37	JP14	JP27	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1355	DRR198449	12F	4846	Tokai	37	JP14	JP27	≤ 0.06	≤ 0.06	≤ 0.06	>128	0.5
PC1356	DRR198450	12F	4846	Kanto	37	JP14	JP27	≤ 0.06	≤ 0.06	≤ 0.06	>128	0.5
PC1364	DRR198451	12F	4846	Tokai	37	JP14	JP27	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1371	DRR198452	12F	6945	Kinki	37	4	23	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1376	DRR198453	12F	4846	Tohoku	37	JP14	JP27	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1382	DRR198454	12F	6945	Tokai	37	4	23	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1384	DRR198455	12F	6945	Sanin	37	4	23	0.12	≤ 0.06	≤ 0.06	≤ 0.06	1
PC1385	DRR198456	12F	4846	Kinki	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1386	DRR198457	12F	4846	Kanto	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1387	DRR198458	12F	6945	Kinki	37	4	23	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1389	DRR198459	12F	4846	Kyusyu	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1390	DRR198460	12F	4846	Kanto	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1394	DRR198461	12F	4846	Sanin	37	JP14	JP27	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1395	DRR198462	12F	4846	Kanto	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1397	DRR198463	12F	6945	Kinki	37	4	23	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1399	DRR198464	12F	6945	Kinki	37	4	23	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1403	DRR198465	12F	4846	Kinki	37	JP14	JP27	0.12	0.12	≤ 0.06	>128	1
PC1407	DRR198466	12F	6945	Sanin	37	4	23	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	1
PC1410	DRR198467	12F	6945	Kinki	37	4	23	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1412	DRR198468	12F	4846	Tohoku	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1416	DRR198469	12F	4846	Sanin	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1426	DRR198470	12F	4846	Tokai	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1429	DRR198471	12F	6945	Kinki	37	4	23	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1438	DRR198472	12F	4846	Tokai	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1442	DRR198473	12F	4846	Tohoku	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1450	DRR198474	12F	4846	Kyusyu	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1465	DRR198475	12F	4846	Tohoku	37	JP14	JP27	0.25	≤ 0.06	≤ 0.06	>128	1
PC1467	DRR198476	12F	4846	Kyusyu	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1499	DRR198477	12F	6945	Kinki	37	4	23	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1532	DRR198479	12F	4846	Tokai	37	JP14	JP58	0.12	≤ 0.06	≤ 0.06	>128	1

Isolate name	Accession No.	Serotype	Sequence type	Region	BBP profile			MIC ($\mu\text{g/ml}$)*				
					<i>bbp1a</i>	<i>bbp2b</i>	<i>bbp2x</i>	PCG	CTX	MEM	EM	LFX
PC1536	DRR198480	12F	6945	Kyusyu	37	4	23	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06	1
PC1538	DRR198481	12F	4846	Tohoku	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1540	DRR198482	12F	4846	Kinki	37	JP14	JP59	0.12	0.5	≤ 0.06	>128	1
PC1544	DRR198483	12F	4846	Kyusyu	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1554	DRR198484	12F	4846	Kyusyu	37	JP14	JP27	0.12	≤ 0.06	≤ 0.06	>128	1
PC1557	DRR198485	12F	4846	Tokai	37	JP14	JP27	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1565	DRR198486	12F	6945	Kinki	37	4	23	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1567	DRR198487	12F	4846	Kanto	37	JP14	JP27	≤ 0.06	≤ 0.06	≤ 0.06	>128	1
PC1568	DRR198488	12F	6945	Kinki	37	4	23	≤ 0.06	≤ 0.06	≤ 0.06	>128	1

*PCG, penicillin; CTX, cefotaxime; MEM, meropenem; EM, erythromycin; LFX, levofloxacin.

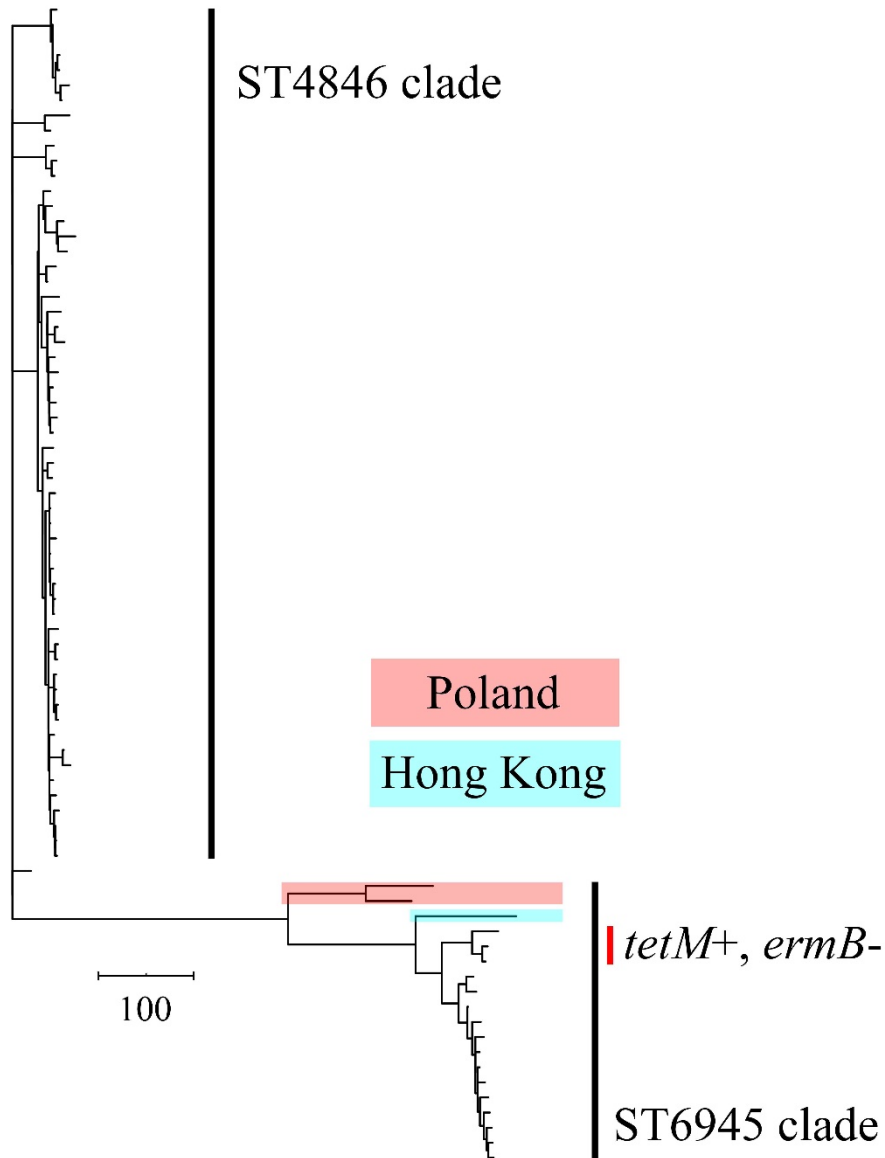
Appendix Table 2. Mapping coverage and genetic characteristics of the isolates tested in this study.

Isolate name	Coverage	N ₅₀	N ₇₀	<i>ermB</i>	<i>ermTR</i>	<i>mef</i>	Pili1	Pili2	<i>folA</i> mutation		<i>folP</i> insertion	<i>tetM</i>	<i>tetO</i>	<i>tet(S/M)</i>
									I100L	D92R				
PC0217	97.7461	64385	45761	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC0786	78.5059	41865	25372	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC0822	78.8616	52525	28169	Yes	No	No	No	No	No	No	Yes	Yes	No	No
PC0827	81.6176	56700	31674	Yes	No	No	No	No	No	No	Yes	Yes	No	No
PC0872	66.3265	40005	21885	Yes	No	No	No	No	No	No	Yes	Yes	No	No
PC0882	71.4055	57474	31674	Yes	No	No	No	No	No	No	Yes	Yes	No	No
PC0896	158.557	60391	34894	Yes	No	No	No	No	No	No	Yes	Yes	No	No
PC0974	68.1011	55241	22704	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1034	126.533	60391	34921	Yes	No	No	No	No	No	No	Yes	Yes	No	No
PC1035	94.4535	63775	33872	Yes	No	No	No	No	No	No	No	Yes	No	No
PC1037	88.866	55241	30257	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1050	76.4846	18220	10453	Yes	No	No	No	No	No	No	No	Yes	No	No
PC1051	167.889	62638	42644	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1053	107.877	63628	36760	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1084	150.26	45969	25243	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1114	45.3837	40266	20946	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1150	61.9118	58103	31855	Yes	No	No	No	No	No	No	No	Yes	No	No
PC1182	129.796	62638	39115	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1185	60.9356	58492	26882	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1198	41.6472	51813	26882	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1203	51.6374	55274	23990	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1266	181.194	51362	26881	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1271	70.983	64206	33804	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1277	136.951	55241	26397	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1278	102.953	45101	24472	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1283	133.917	60391	34921	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1285	188.722	59453	43996	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1286	93.991	72107	42926	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1287	77.8085	59498	42926	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1293	148.198	57257	34280	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1296	66.2212	60385	34921	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1305	112.115	62638	39352	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1314	151.22	48407	28569	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1347	103.943	58827	37231	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1350	84.8507	58836	33812	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1355	85.4997	14795	8189	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1356	72.7795	60395	41736	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1364	87.9509	70612	51434	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1371	77.9551	45103	23126	Yes	No	No	No	No	No	No	No	Yes	No	No
PC1376	75.953	65767	45623	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1382	111.501	56760	26157	Yes	No	No	No	No	No	No	No	Yes	No	No
PC1384	87.6827	48436	24384	No	No	No	No	No	No	No	No	Yes	No	No
PC1385	93.9111	52230	28116	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1386	111.589	54898	23990	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1387	95.3195	51531	24460	Yes	No	No	No	No	No	No	No	Yes	No	No
PC1389	91.3471	57257	25061	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1390	54.8823	34473	18090	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1394	103.749	59543	34948	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1395	73.0218	59498	28213	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1397	101.411	60389	31592	Yes	No	No	No	No	No	No	No	Yes	No	No
PC1399	111.571	62636	33870	Yes	No	No	No	No	No	No	No	Yes	No	No
PC1403	93.9766	46763	25061	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No

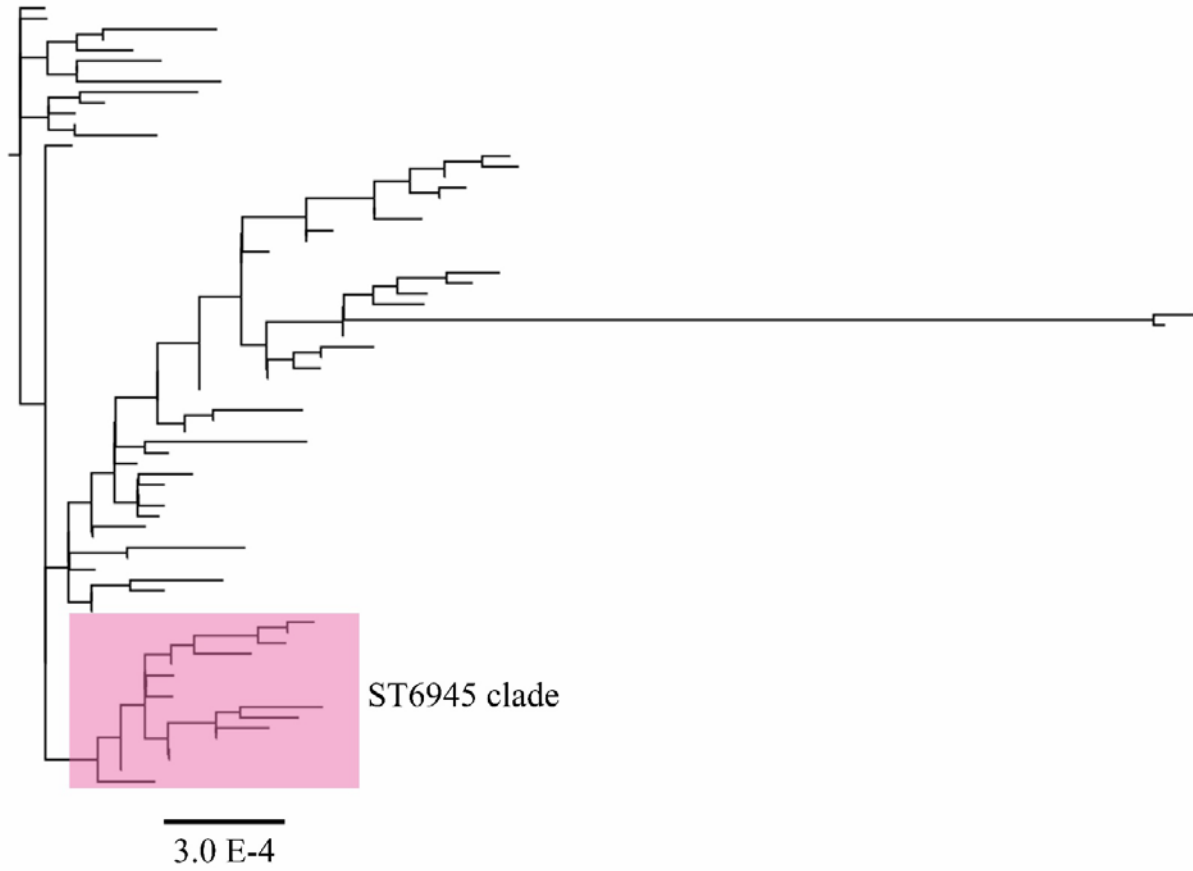
Isolate name	Coverage	N ₅₀	N ₇₀	<i>ermB</i>	<i>ermTR</i>	<i>mef</i>	Pili1	Pili2	<i>folA</i> mutation		<i>folP</i> insertion	<i>tetM</i>	<i>tetO</i>	<i>tet(S/M)</i>
									I100L	D92R				
PC1407	82.8333	45091	24010	No	No	No	No	No	No	No	No	Yes	No	No
PC1410	103.535	63775	33857	Yes	No	No	No	No	No	No	No	Yes	No	No
PC1412	88.8179	60388	31674	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1416	146.909	54108	26882	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1426	107.283	45091	23950	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1429	137.678	54628	25068	Yes	No	No	No	No	No	No	No	Yes	No	No
PC1438	136.557	41446	20566	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1442	140.574	55211	24257	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1450	145.005	61471	34081	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1465	151.159	65767	34871	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1467	104.569	51362	24011	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1499	128.857	63775	34488	Yes	No	No	No	No	NA	NA	No	Yes	No	No
PC1532	217.819	56132	30642	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1536	75.7587	59643	28863	No	No	No	No	No	No	No	No	Yes	No	No
PC1538	89.3087	60942	42997	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1540	95.9846	108974	63109	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1544	184.055	97606	69764	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1554	112.844	122409	60696	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1557	108.202	87034	53299	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1565	107.677	85128	48044	Yes	No	No	No	No	No	No	No	Yes	No	No
PC1567	135.756	93700	60031	Yes	No	No	No	No	Yes	No	Yes	Yes	No	No
PC1568	162.995	90146	65028	Yes	No	No	No	No	No	No	No	Yes	No	No

Appendix Table 3. Five genes that were identified exclusively in PC-JP12F isolates

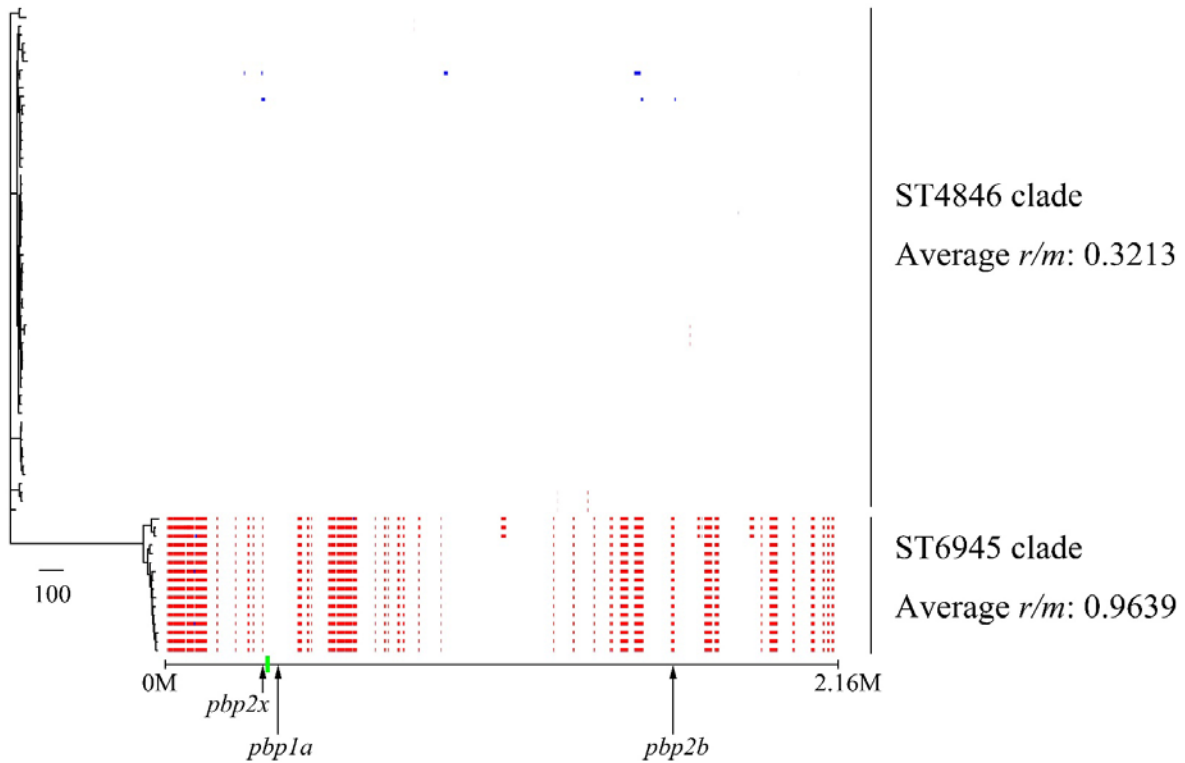
Protein name	Sequence ID
Uncharacterized protein, Uncharacterized protein, NTP pyrophosphohydrolase including oxidative damage repair enzymes	CKV79152.1, CKW99395.1, VKN64777.1
Uncharacterized protein, Uncharacterized protein, Uncharacterized protein, Uncharacterized protein, Hypothetical protein	CIS34299.1, CIT10688.1, CIU07372.1, CIV31640.1, CIZ29293.1, BBG82149.1
Hypothetical protein SP2UMMC_09170	KAA00665.1
Putative membrane protein, Membrane protein, Membrane protein, Uncharacterized protein, Uncharacterized protein	EJG79121.1, KAA03079.1, KAA03160.1, CEO70970.1, CEV43084.1



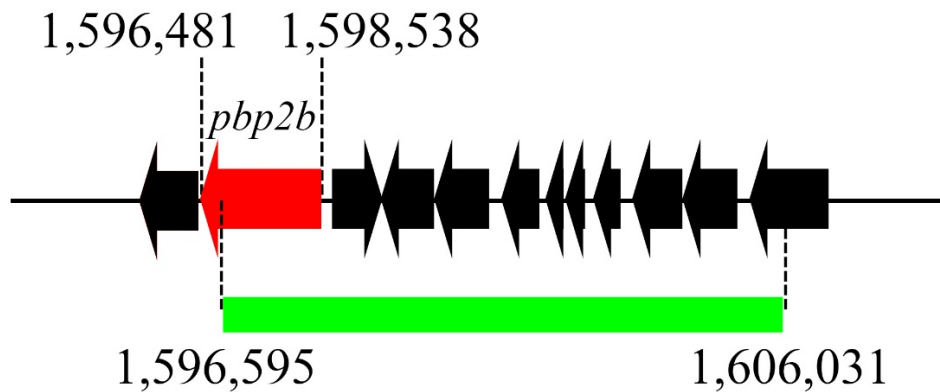
Appendix Figure 1. Recombination-free maximum-likelihood tree of serotype 12F-CC4846 isolates and three GPCS334 isolates from Poland and Hong Kong. All three isolates were clustered into an ST6945 clade. Two isolates from Poland carried neither *tetM* nor *ermB*. Three isolates in a ST6945 clade from Japan, marked with a red line, did not carry *ermB*.

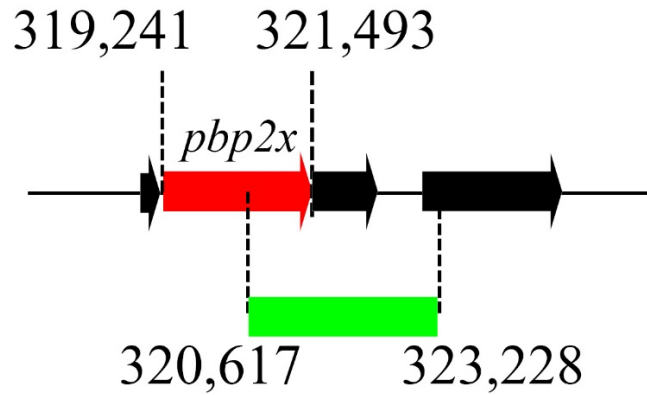


Appendix Figure 2. Maximum likelihood phylogenetic tree of serotype 12F *cps* locus sequences. The ST6945 isolates were exclusively included in the same cluster.

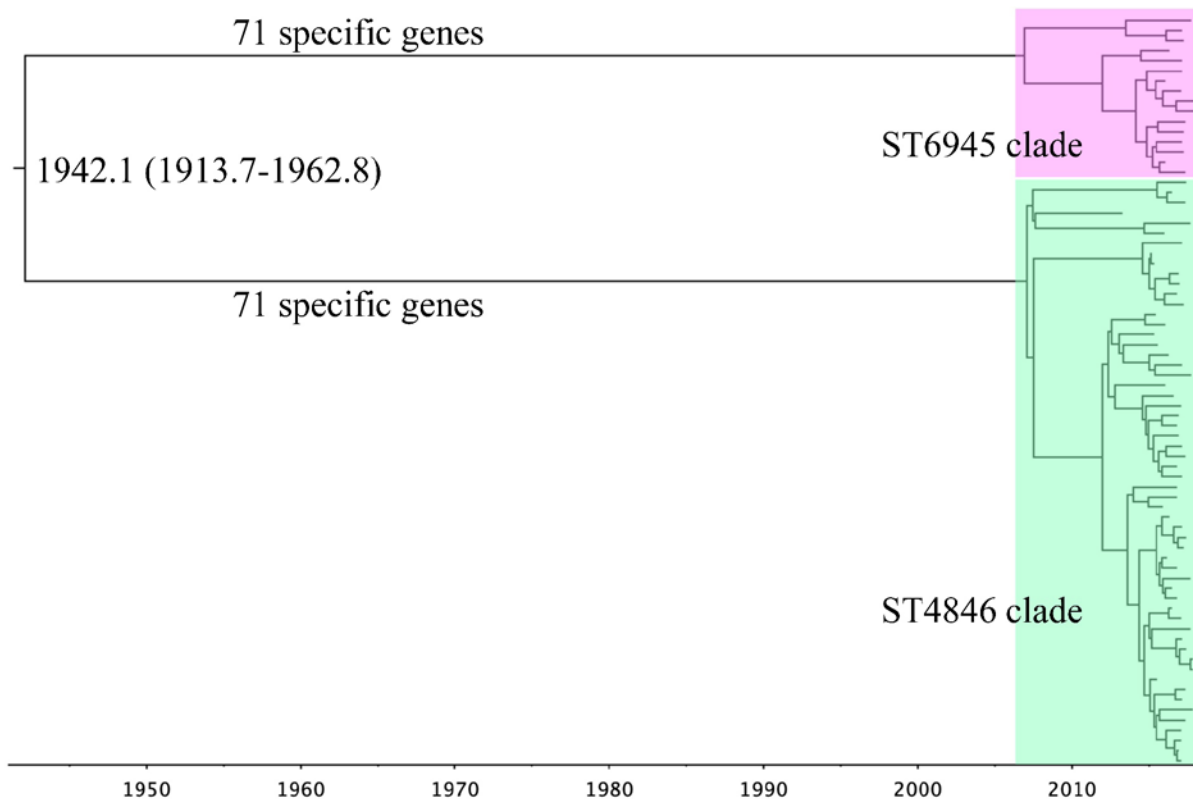


Appendix Figure 3. Phylogenetic tree and predicted recombination sites generated with Gubbins for serotype 12F isolates recovered in Japan. The blue blocks are unique to a single isolate, whereas the red blocks are shared by multiple isolates. The horizontal position of the blocks represents their position in the reference *S. pneumoniae* ASP0581 sequence (GenBank accession No. NZ_AP019192.2). The light green box on the coordinate line shows the *cps* locus of *S. pneumoniae* ASP0581 (GenBank accession No. NZ_AP019192.2), which was used as the reference sequence for mapping.



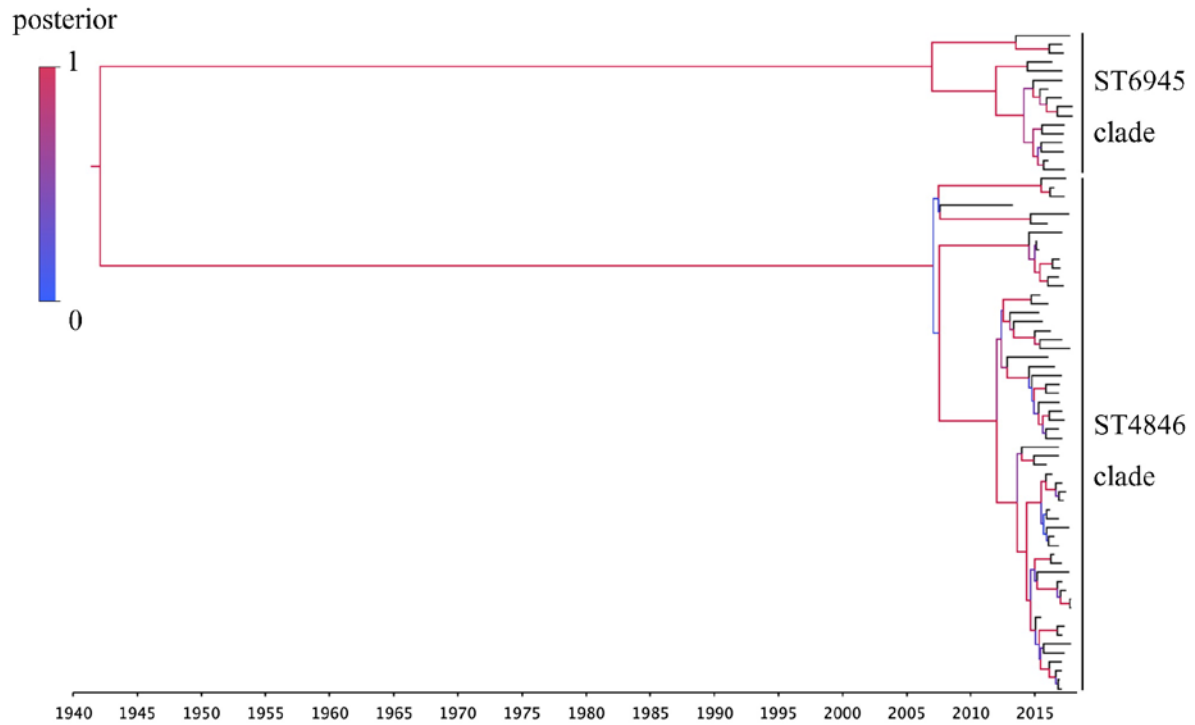


Appendix Figure 4. Sketch of the predicted recombination sites, including *pbp2b* and *pbp2x*. The light green blocks show the recombination sites. Each number shows the sequence coordinates based on *S. pneumoniae* ASP0581 (GenBank accession No. NZ_AP019192.2). These two recombination sites were shared by all of the ST6945 isolates.

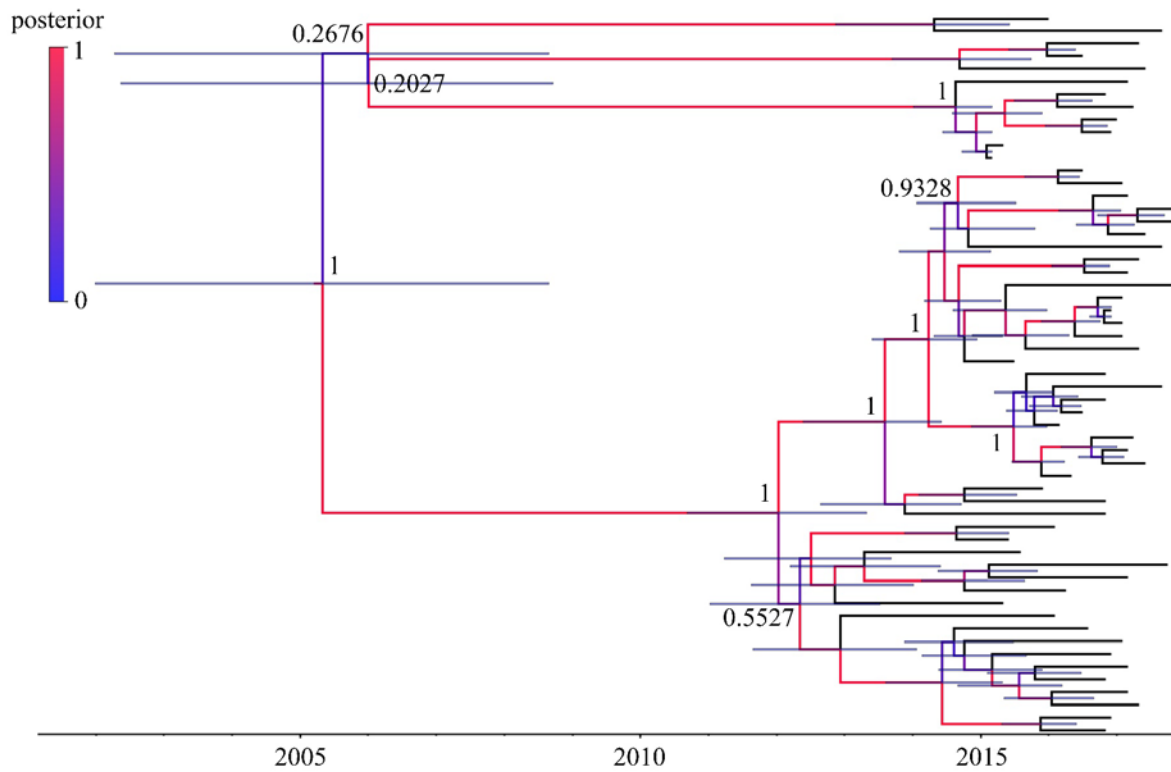


Appendix Figure 5. Maximum clade credibility tree of serotype 12F-CC4846 isolates in Japan created by BEAST. The time of the most recent common ancestor (TMRCA) is shown on the tree with 95% HPD.

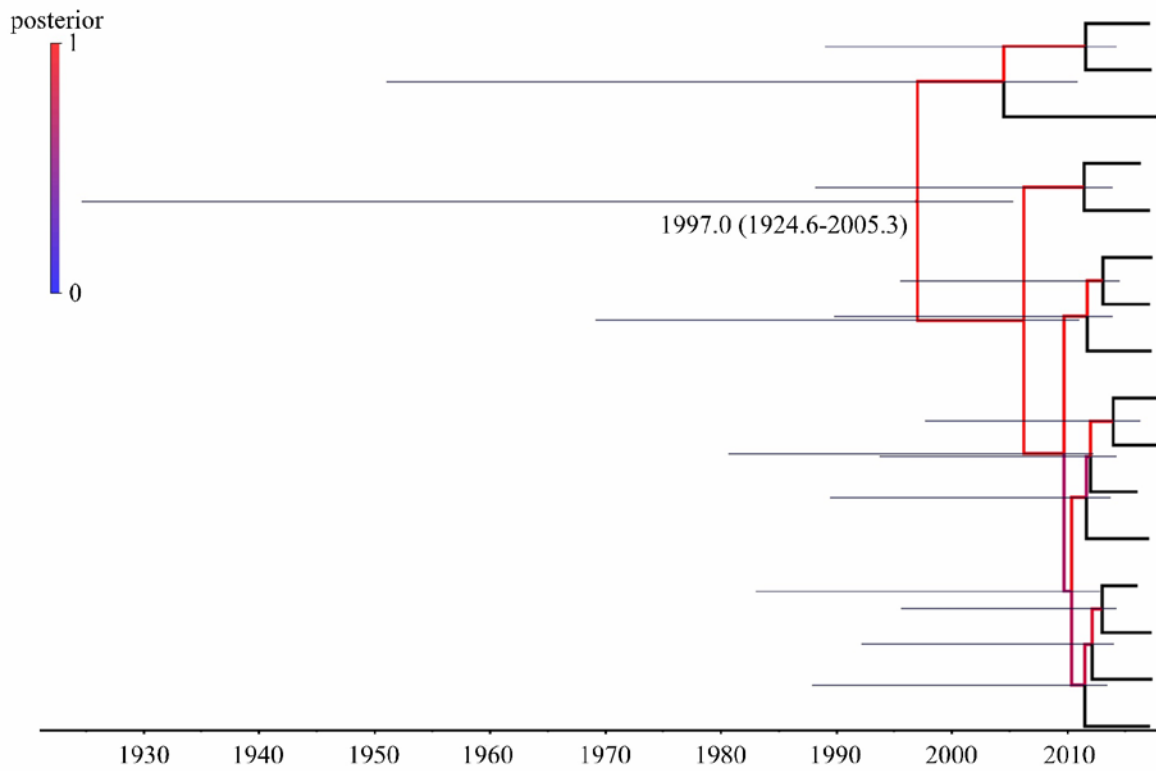
The ST6945 and ST4846 isolates included in the clades are highlighted in pink and light green, respectively.



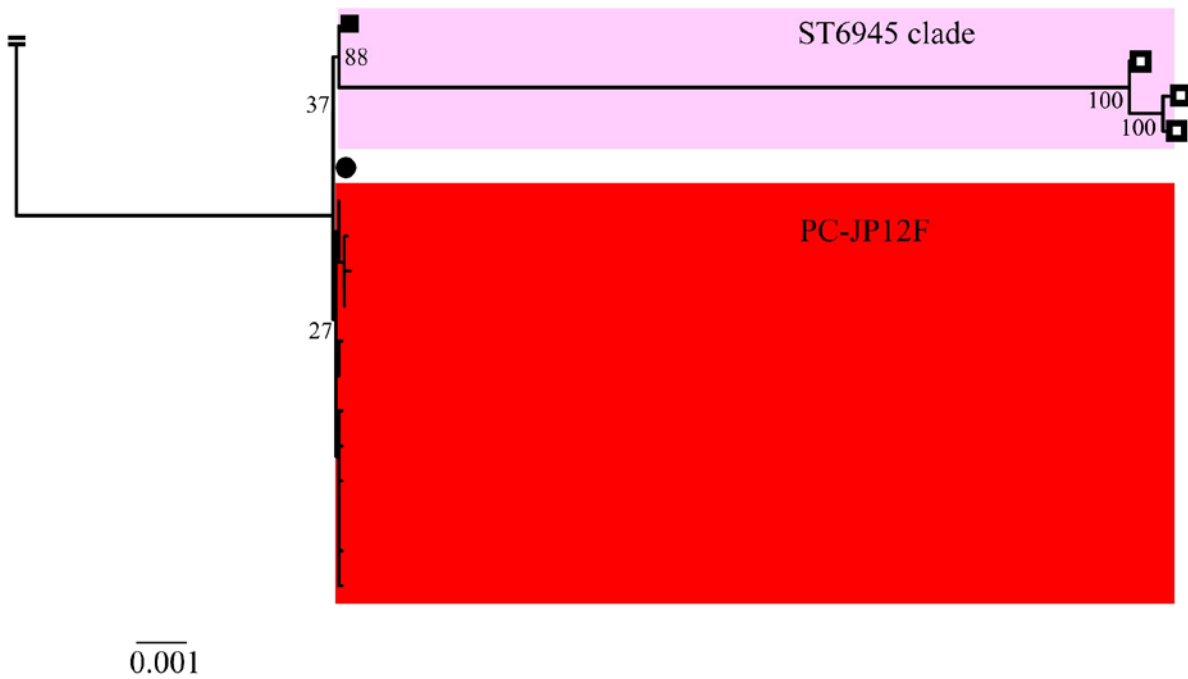
Appendix Figure 6. Maximum clade credibility tree of the serotype 12F-CC4846 isolates recovered in Japan created by BEAST. The posterior probabilities for each branch are included.



Appendix Figure 7. Maximum clade credibility tree of ST4846 clade isolates created by BEAST. The posterior probabilities of each branch are shown. The blue bars on each node indicate 95% HPD of the times of the most recent common ancestor (TMRCA). The numbers on the branches indicate the posterior probabilities.



Appendix Figure 8. Maximum clade credibility tree of the ST6945 clade isolates created by BEAST. The posterior probabilities of each branch are shown. The time of the most recent common ancestor (TMRCA) is shown on the tree with 95% HPD. The blue bars on each node indicate 95% HPD of the TMRCA.



Appendix Figure 9. Phylogenetic tree of the *Tn916* region of serotype 12F-CC4846 isolates recovered in Japan. The reference sequence of *Tn916* (GenBank accession No. U09422.1) was used for the outgroup. All the isolates shown in pink are ST6945 isolates, and all the isolates shown in red are PC-JP12F isolates. A black square includes all 13 serotype 12F-ST6945 isolates with *ermB*, and each white square indicates a 12F-ST6945 isolate without *ermB*. A black circle indicates all 13 serotype 12F-ST4846 isolates except PC-JP12F isolates. The numbers on branches indicate bootstrap values.