

Table S1. Genes involved in the transcriptomic response of *S. pneumoniae* to treatment with 8 μ M seconeolitsine.

spr code	Protein ^a	Gene	Cluster	Leader/ leading	Relative fold variation detected by ^b				
					RNASeq		Microarrays		
					t5	t15	t5	t15	t30
0001	Chromosome replication initiation protein	<i>dnaA</i>	1	→		2.0			
0005	Peptidyl-tRNA hydrolase	<i>pth</i>	1	→	3.2	2.3			
0006	Transcription-repair coupling factor	<i>mfd</i>	1	→	3.0	2.2	2.9	2.8	
0007	Conserved hypothetical		1	→	2.0				
0008	Hypothetical		1	→	2.6	2.0			
0009	Conserved hypothetical		1	→	2.7	2.2			
0010	Conserved hypothetical		1	→	2.6	2.1	2.3	2.3	
0012	ATP-dependent zinc metalloprotease	<i>ftsH</i>	1	→	2.0				
0013	Competence-specific transcription modulator	<i>comX</i>	1	→			9.6	9.8	
0014	Transposase		1	→	2.0		4.0	4.3	
0016	Transposase		1	→	3.1	2.7			
0017	Degenerate transposase		1	←	5.3	4.9	3.6		
0018	Degenerate transposase		1	←	6.5	5.4	3.7	3.7	-3.3
0019	Degenerate transposase		1	←	6.2	5.9	3.3	3.2	-2.9
0022	Conserved hypothetical								-3.7
0030	Hypothetical						2.1		
0031	Hypothetical						4.0		
0032	DNA polymerase I	<i>polA</i>			-4.9	-2.9	-4.0	-3.9	
0033	Conserved hypothetical				-4.0	-3.6			
0034	Conserved hypothetical				-8.9	-4.6			
0043	Competence factor transporting ATP-binding protein	<i>comA</i>					8.3	8.2	
0044	Competence factor transport protein	<i>comB</i>					9.5		
0045	P-ribosylaminoimidazole-succinocarboxamide synthase	<i>purC</i>					4.5	4.3	
0054	P-ribosyl glucinamide formyltransferase	<i>purK</i>			-2.3				
0055	Hypothetical				-2.5				
0056	Adenylosuccinate lyase	<i>purB</i>			-2.5				
0059	Beta-galactosidase 3	<i>bgaC</i>			-2.5				
0068	Conserved hypothetical				-4.4	-2.8	-3.9	-3.9	
0069	Hypothetical				-4.7		-4.3	-4.2	
0070	Transporter membrane-spanning protein-K+	<i>trkH</i>			-2.3				
0071	Transporter NAD+ binding protein-K+	<i>trkA</i>			-2.3		-2.7	-2.6	
0076	Response regulator	<i>rr08</i>			-3.9	-3.3	-3.1	-2.9	
0077	Histidine kinase	<i>hk08</i>			-3.5	-2.7			
0079	Degenerate transposase						3.9	4.2	
0088	Hypothetical				-2.7				
0089	Conserved hypothetical				-2.5				
0090	Conserved hypothetical				-5.4	-3.9		-4.2	
0099	ABCT membrane-spanning permease-amino acid						-2.2	-2.1	
0101	ABCT solute-binding protein-amino acid				-4.2	-3.0			
0102	Arg-succinate synthase	<i>argG</i>			-5.8	-3.8			

0103	Arg-succinate lyase	<i>argH</i>			-6.5	-5.0		
0104	Hypothetical				-4.1			
0105	Transporter, truncation							-2.1
0110	Hypothetical							-2.1
0113	Hypothetical						-2.1	-2.1
0121	Surface protein PspA	<i>pspA</i>			-2.4			
0122	tRNA (5-methylaminomethyl-2-thiouridylate)-methyltransferase	<i>mnmA</i>			-3.6	-4.0		
0123	Conserved hypothetical				-2.4	-2.7		
0124	tRNA uridine 5-carboxymethylaminomethyl modification	<i>gidA</i>			-2.4	-2.9		
0127	Bacteriocin GG peptide	<i>cibB</i>			2.1			
0128	Bacteriocin GG peptide	<i>cibA</i>					36.3	35.6
0130	Ribosomal protein Ala acetyltransferase	<i>rimI</i>			-2.2		-2.3	-2.2
0146	ABCT substrate-binding-amino acid				-2.5	-2.1	-2.3	-2.2
0157	Conserved hypothetical				2.4	2.3		
0158	Hypothetical				4.7	4.7		2.0
0159	Conserved hypothetical				4.4	3.7	3.1	3.2
0161	Riboflavin synthase beta chain	<i>ribH</i>			5.0	4.8	2.8	2.7
0162	Riboflavin biosynthesis; GTP-cyclohydrolase II.	<i>ribA</i>			4.4	4.3	3.1	3.0
0163	Riboflavin synthase alpha-chain	<i>ribC</i>			4.2	4.1	2.6	2.6
0164	Riboflavin biosynthesis; a deaminase	<i>ribD</i>			3.7	3.6	2.0	2.0
0173	Arsenate reductase	<i>arsC</i>			2.1		2.2	2.2
0174	Hypothetical				3.3	2.4	2.6	2.5
0178	Dihydrofolate:folylpoly-Glu synthase	<i>folC</i>			2.9	2.5	2.3	2.3
0179	Hypothetical				2.2			
0180	Cardiolipin synthase	<i>cls</i>			2.1			
0181	Hypothetical	<i>orf47</i>					3.5	3.4
0184	Hypothetical				2.0			
0185	Ribonucleoside-tri-P reductase activating protein	<i>nrdG</i>			2.0			
0186	Hypothetical				1.9			
0218	Conserved hypothetical				-1.9			
0224	ABCT substrate-binding-iron							2.2
0236	Conserved hypothetical				-3.1	-2.6		
0237	Conserved hypothetical				-3.3			
0244	6-P-beta-glucosidase	<i>bglA</i>			1.9	2.2		
0245	L-Gln-D-fructose-6-P-amidotransferase	<i>glmS</i>			-7.6	-6.9		
0247	LPxTG protein. Alkaline amylopullulanase	<i>spuA</i>			-7.4	-5.4		
0251	DNA polymerase III, alpha subunit	<i>polC</i>			1.9			
0254	Aminopeptidase	<i>pepS</i>	8	→			-2.0	-2.0
0257	Hypothetical		8	→	-3.0			
0258	Aminopeptidase C	<i>pepC</i>	8	→	-4.5	-4.3		
0259	PTS mannose-specific EIID	<i>manN</i>	8	←	-3.0			
0260	PTS mannose-specific EIIC	<i>manM</i>	8	←	-3.0			
0261	PTS mannose-specific EIIB	<i>manL</i>	8	←	-2.7			
0262	Alcohol DH	<i>adhP</i>	8	←	-8.3	-3.1		
0263	Conserved hypothetical		8	←	-4.7	-2.5		
0266	Dihydropteroate synthase	<i>sulA</i>	8	→	-2.0			
0270	Hypothetical				-7.1	-4.5		

0426	Trk transporter membrane-spanning protein-K+	<i>trkH</i>	-5.4	-2.9		
0427	Trk NAD ⁺ binding protein-K+	<i>trkA</i>	-5.1	-3.1		
0428	Conserved hypothetical		-2.8		-2.6	
0429	Conserved hypothetical		-2.7			
0434	Conserved hypothetical		1.9			
0436	Hypothetical		1.9			
0437	RNA polymerase delta subunit	<i>rpoE</i>	2.6	2.0		
0439	Conserved hypothetical		-2.3			
0445	Type I restriction enzyme	<i>hsdS</i>	2.2	2.6	2.0	
0446	Type I restriction enzyme specificity protein	<i>hsdS</i>	2.3	2.6		
0459	ABCT ATP-binding protein					3.6
0460	ABCT membrane-spanning permease		-1.9			4.4
0462	Regulatory protein	<i>spiR1</i>	-2.4			
0465	Peptide pheromone, bacteriocin-like peptide	<i>spiP</i>				2.7
0470	Bacteriocine-like	<i>pncW</i>			2.1	3.3
0471	CAAX protease	<i>pncO</i>				3.0
0472	Immunity protein	<i>pncQ</i>				2.8
0473	CAAX protease	<i>pncP</i>		2.2		
0474	ABCT ATP binding protein			2.5		2.9
0477	Conserved hypothetical		1.9			
0479	Conserved hypothetical		1.8			
0480	Conserved hypothetical		2.1			
0483	Conserved hypothetical		7.6			
0484	Hypothetical				2.3	
0485	Hypothetical				-2.0	
0486	Conserved hypothetical		-2.2	-2.2		
0489	Hypothetical		-2.1			
0490	Conserved hypothetical		-2.3			
0491	Hypothetical		-2.2	-2.0		
0492	Valyl-tRNA synthetase	<i>valS</i>	-2.2	-2.1		
0497	Degenerate transposase				3.3	3.1
0498	Degenerate transposase				4.5	4.3
0499	Hypothetical		-3.9	-3.3	-2.0	
0502	Hypothetical		-4.0			
0503	Hypothetical		-3.2		-2.6	-2.8
0507	Phe-tRNA synthase alpha chain	<i>pheS</i>	-2.8	-1.9		
0508	Conserved hypothetical		-2.4			
0509	Phe-tRNA synthase beta chain	<i>pheT</i>	-2.8	-2.0		
0510	Hypothetical		-5.5	-3.5	-4.3	
0511	Degenerate transposase					-2.0
0514	Tetrahydropteroyltri-Glu methyltransferase	<i>metE</i>	-4.0	-3.2		
0515	5,10-methylenetetrahydrofolate reductase	<i>metF</i>	-3.7			
0524	ABCT membrane-spanning permease-peptide	<i>vex1</i>	2.6	2.3		
0526	ABCT membrane-spanning permease-peptide	<i>vex3</i>	2.6	2.3		
0530	Fructose-bi-P aldolase	<i>fba</i>	2.1			
0531	Hypothetical		4.2	3.0	3.6	3.6
0532	ABCT membrane-spanning permease-Gln	<i>glnP</i>	4.0	3.3		

0533	ABCT membrane-spanning permease-Gln	<i>glnP</i>			4.4	3.4			
0536	ABCT ATP-binding protein-Gln	<i>glnH</i>			3.1				
0537	Single-stranded DNA-specific exonuclease	<i>recJ</i>				-1.9			
0539	Tributylin esterase	<i>estA</i>			3.0	2.9			
0542	Hypothetical				2.3	2.0	2.5	2.5	
0557	ABCT ATP-binding protein				-2.8	-3.0			
0558	Conserved hypothetical				-2.7	-2.9			
0559	Conserved hypothetical				-2.8	-2.8			
0560	Hypothetical				-2.2				
0562	PTS sugar-specific EII component				-2.8				
0563	Hypothetical				-2.4				
0568	Hypothetical				-2.6				
0578	Response regulator	<i>rr09</i>			-2.5	-2.2			
0579	Histidine kinase	<i>hk09</i>			-2.4				
0585	Thymidylate synthase	<i>thyA</i>			-2.8	-2.6			
0599	Hypothetical						-2.3	-2.4	
0613	Orotidine-5-decarboxylase	<i>pyrF</i>			-3.1	-2.3			
0614	Orotate P-ribosyltransferase	<i>pyrE</i>						-2.4	
0620	ABCT substrate-binding protein							2.5	
0621	ABCT substrate-binding protein							2.4	
0628	Conserved hypothetical		3	→	3.9				
0629	Hydroxyethylthiazole kinase	<i>thiM</i>	3	→	4.2				
0630	Thiamin-P pyrophosphorylase	<i>thiE</i>	3	→	4.8				
0631	Conserved hypothetical		3	→	6.6		2.5	2.6	
0632	ABCT ATP-binding protein		3	→	7.4	3.6	4.8	4.8	
0633	Conserved hypothetical		3	→	9.4	4.9	6.6	6.3	
0634	Transcriptional regulator	<i>tenA</i>	3	→	13.3	5.9	6.1	6.0	2.9
0635	Hypothetical		3	→	15.1	6.9	2.6	2.7	
0636	Hydroxyethylthiazole kinase	<i>thiM</i>	3	→	9.3	4.2	4.4	4.2	
0637	Thiamine-P pyrophosphorylase	<i>thiE</i>	3	→	12.8	5.1	3.9	4.0	
0639	COPAB ATPases metal repressor	<i>copY</i>	3	→		3.1			
0645	Hypothetical						2.2	2.2	
0646	P-beta-gluco or galactosidase	<i>bgl</i>			6.9				
0652	Conserved hypothetical					-2.1			
0653	Conserved hypothetical				-2.9				
0655	Uracil P-ribosyltransferase	<i>upp</i>			2.5				
0665	Peptide chain release factor 2	<i>prfB</i>			1.9				
0666	ABCT ATP-binding protein	<i>ftsE</i>			2.1				
0667	Cell division	<i>ftsX</i>			2.3				
0669	Hypothetical				2.7				
0690	Conserved hypothetical						2.5	2.5	
0692	Glutathione oxidoreductase	<i>gor</i>			-2.4	-2.7			
0697	Conserved hypothetical				2.9	2.9			
0698	Conserved hypothetical				3.5	3.1	2.1	2.1	
0699	Conserved hypothetical				2.2	2.1		2.3	2.2
0707	Response regulator, transcriptional regulator	<i>ciaR</i>			3.5	3.2	2.8	2.8	
0708	Sensor histide kinase CiaH	<i>ciaH</i>			3.5	2.8	3.1	3.0	
0714	P-glycolate phosphatase	<i>gph</i>			3.2	2.8			

0715	DNA gyrase subunit B	<i>gyrB</i>			2.7	2.2			
0716	Cell division regulator	<i>ezrA</i>			2.3				
0717	Transposase				5.4	3.9			
0718	Transposase				5.2	3.8	3.1	3.1	
0720	Hypothetical								2.0
0721	Conserved hypothetical				8.5	6.7	4.7	4.6	
0722	Transposase						4.2	4.5	
0723	Degenerate transposase							2.1	
0725	ATP dependent protease				-2.3	-2.0			
0728	ABCT ATP-binding protein-Gln	<i>glnQ</i>			-2.0	-2.0			
0744	Pyrimidine nucleoside phosphorylase	<i>pdp</i>	4	→	1.9				
0745	Deoxyribose-phosphate aldolase	<i>deoC</i>	4	→	1.9				
0746	Cytidine deaminase	<i>cdd</i>	4	→	2.0				
0747	Conserved hypothetical		4	→	2.2				
0748	ABCT ATP-binding-ribose/galactose		4	→	2.4		2.1	2.1	
0749	ABCT membrane-spanning permease-ribose/galactose		4	→	2.1				
0750	ABCT membrane-spanning permease-ribose/galactose		4	→	2.1				
0751	Degenerate transposase (orf1)		4	→	5.3	4.3	4.3	4.4	
0752	Degenerate transposase (orf1)		4	→	3.2		3.6	3.6	
0753	Degenerate transposase (orf2)		4	→	4.0	3.3	2.8	2.8	
0754	Degenerate transposase (orf2)		4	→	3.6		2.5	2.6	
0765	Degenerate transposase (orf2)				3.0				
0766	Degenerate transposase (orf2)				4.3	1.9			
0767	Transposase (orf1)				3.6				
0771	ABCT ATP-binding-unknown substrate				2.0				
0773	Conserved hypothetical				2.2				
0775	Conserved hypothetical				2.6				
0778	Transcriptional repressor of the fructose operon	<i>fruR</i>			-2.9	-2.2			
0779	Fructose-1-P kinase	<i>fruB</i>			-2.7	-2.1			
0780	Fructose specific-P-transferase system IIBC component	<i>fruA</i>			-2.0				
0782	Hypothetical				-3.3	-3.2			
0783	Probable pyridoxal-P dependent aminotransferase				-2.1	-2.2			
0784	Thiamin biosynthesis	<i>thil</i>					-2.5	-2.5	
0785	Hypothetical								-2.0
0788	Hypothetical						-2.0	-2.0	
0798	Hypothetical						2.1	2.1	
0812	ABCT ATP-binding-unknown substrate						2.6	2.6	
0815	Degenerate transposase								-2.0
0830	23S rRNA pseudouridine synthase	<i>rluD</i>			1.8				
0831	Choline binding protein E	<i>cbpE</i>			2.0				
0839	Conserved hypothetical				2.3				
0856	DNA-binding, bind donor DNA	<i>comEA</i>					10.2	10.7	
0857	DNA entry pore	<i>comEC</i>					14.0	14.1	
0858	Hypothetical						3.2	3.2	
0859	Hypothetical						3.4	3.4	
0860	Hypothetical						4.4	4.4	

0865	Dihydroorotate DH electron transfer subunit	<i>pyrK</i>					4.2
0868	Fibronectin-binding protein-like protein A	<i>flpA</i>	-3.2	-2.8	-2.8	-2.9	
0869	Conserved hypothetical		-2.5	-2.4			
0872	Formamidopyrimidine-DNA glycosylase	<i>mutM</i>			-2.1		
0873	Conserved hypothetical		-2.1			-2.1	
0881	DNA postentry processing protein	<i>coiA</i>			6.4	6.0	
0886	Degenerate transposase (orf1)		6.6		4.5	4.3	
0898	Degenerative transposase				2.6	2.9	
0904	Conserved hypothetical			-2.4			
0905	Cationic amino acid transporter - APC Superfamily			-2.0			
0906	Lipoprotein	<i>lmb</i>		-2.0			
0909	Hypothetical						-2.1
0910	Pneumococcal histidine triad protein E precursor	<i>phtE</i>					-3.2
0914	Ferrochelatase	<i>hemH</i>	-4.9	-3.6			-3.7
0915	Large conductance mechano-sensitive ion channel	<i>mscL</i>	-4.8	-4.7			
0917	Citrulline cluster-linked gene	<i>ccl</i>	-3.1	-3.1	-2.4	-2.3	
0918	Asp beta-semialdehyde DH	<i>asd</i>	-2.2	-2.3			
0933	Hypothetical		2.7				
0934	ABCT substrate-binding-iron	<i>piaA</i>		-2.4			
0940	Hypothetical		2.1				
0943	Hypothetical						-2.3
0980	Conserved hypothetical		2.0				
0981	Glycosyltransferase	<i>cpoA</i>	2.0				
0982	Conserved hypothetical		2.1	2.0			
0983	Hypothetical		3.1	2.8			
0987	Degenerate transposase		4.2				
0988	Transposase		3.5				
0993	Degenerate transposase		3.1		2.7	2.7	
0996	DNA repair protein	<i>radC</i>			4.8	4.6	
0997	Conserved hypothetical				3.1	3.0	
0998	Conserved hypothetical		2.0				
0999	Hypothetical		2.5		2.4	2.5	
1017	Riboflavin biosynthesis protein	<i>mreA</i>	2.1		3.2	3.2	
1018	Conserved hypothetical				2.7	2.6	
1023	ABCT membrane-spanning permease		2.0	2.3			
1026	Hypothetical				-3.9	-4.1	
1028	Glyceraldehyde-3-P DH	<i>gapN</i>	-3.6				
1043	Conserved hypothetical		-2.8	-2.3			
1044	Ribonuclease HII	<i>rnhB</i>	-2.5				
1045	Conserved hypothetical		-2.1	-2.0			
1061	Pneumococcal histidine triad protein A	<i>phtA</i>	3.1	2.2	2.1	2.2	
1064	Glutaredoxin-like protein	<i>nrdH</i>	4.4		2.1	2.1	
1065	Ribonucleoside-diphosphate reductase, subunit alpha	<i>nrdE</i>	3.9		2.6	3.0	
1066	Ribonucleoside-diP reductase 2, subunit beta	<i>nrdF</i>	4.5	2.2	3.3	3.9	
1070	PTS system, lactose-specific IIBC component	<i>lacE</i>	-3.9	-3.1			
1071	PTS system, lactose-specific IIA component	<i>lacF</i>	-5.2				

1072	Antiterminator	<i>lacT</i>			-4.5	-3.8		
1073	Tagatose 1,6-diphosphate aldolase	<i>lacD</i>			-3.3	-2.5		
1074	Tagatose-6-P kinase	<i>lacC</i>			-3.2			
1075	Galactose-6-P isomerase LacB subunit	<i>lacB</i>					-2.2	-2.3
1076	Galactose-6-P isomerase LacA subunit	<i>lacA</i>			-3.1			
1091	Hypothetical				-3.4		-2.5	-2.5
1094	Conserved hypothetical				-2.0			
1098	Sortase	<i>srtA</i>			1.9			
1109	Formate-tetrahydrofolate ligase	<i>fhs</i>			1.9	1.8		
1120	ABCT membrane spanning permease-Gln	<i>glnP</i>			4.1	3.1		
1121	ABCT ATP-binding-Gln	<i>glnQ</i>			3.0	2.6		
1122	Glucose-6-P-1-DH	<i>zwf</i>			4.0	3.1	2.2	2.5
1129	Hypothetical		10	←	-2.8			
1130	Hypothetical		10	←	-2.7			
1135	3-isopropylmalate DH	<i>leuB</i>	10	←	-2.7			
1136	2-isopropylmalate synthase	<i>leuA</i>	10	←	-3.0			
1137	2-isopropylmalate synthase	<i>leuA</i>	10	←	-2.8			
1138	Hypothetical		10	←	-2.9			
1139	Copper sensitivity	<i>cutC</i>	10	←	-3.3	-2.3		
1140	Conserved hypothetical		10	←	-2.6			
1141	DNA topoisomerase I	<i>topA</i>	10	←	-6.2	-5.4	-3.6	-3.6
1142	Conserved hypothetical		10	←	-2.7	-2.5		
1150	Conserved hypothetical				-3.1	-2.3		
1151	Required for phosphorylcholine incorporation in teichoic and lipoteichoic acids	<i>licD1</i>			-3.1	-2.5	-2.3	-2.3
1152	licD Protein	<i>licD2</i>			-2.6		-2.3	-2.2
1172	CrcB protein	<i>crcB</i>			-2.5		-2.0	-2.0
1173	CrcB protein	<i>crcB</i>					-2.0	
1176	Conserved hypothetical				-3.1			
1182	Hypothetical				-2.2	-2.8		
1183	ABCT ATP-binding protein				-2.6	-3.2		
1194	ABCT substrate-binding protein - oligopeptide	<i>appA</i>				-3.3		
1195	Conserved hypothetical					-2.9		
1197	Degenerate transposase (orf2)				-2.8	-3.1		
1201	Hypothetical				-4.7	-3.5		
1202	ABCT ATP-binding protein-unknown substrate				-5.2	-4.7		
1203	ABCT ATP-binding/membrane spanning protein				-5.2	-4.9		
1204	Prolyl oligopeptidase	<i>ptrB</i>			-5.1	-4.6	-2.6	-2.7
1205	Conserved hypothetical				-4.3	-5.1	-2.5	-2.5
1207	Hypothetical							-3.1
1208	Hypothetical							-3.0
1237	Hypothetical							-2.1
1238	ABCT ATP-binding protein-unknown substrate						-2.9	-4.7
1250	Conserved hypothetical				-2.7			
1251	ABCT substrate-binding-Gln	<i>glnH</i>			-2.6	-2.3		
1252	Phosphate transport system regulatory protein	<i>phoU</i>					-2.2	-2.3

1253	ABCT ATP-binding-P	<i>pstB1</i>			-2.3	-2.1		-2.3
1254	ABCT ATP-binding-P	<i>pstB2</i>			-2.3	-2.2		
1255	ABCT membrane-spanning permease-P	<i>pstA</i>			-2.3	-2.2	-3.3	-3.5
1256	ABCT membrane-spanning permease-P	<i>pstC</i>			-2.6	-2.4		
1257	ABCT substrate-binding-P	<i>pstS1</i>			-2.6	-2.3		
1270	Ser-P kinase/phosphatase	<i>hprK</i>			1.8			
1292	Conserved hypothetical				-3.1	-2.6		
1301	Conserved hypothetical						2.0	2.0
1310	Peptide deformylase	<i>fms</i>			-2.9	-2.8		
1314	ABCT ATP-binding-Asp/Glu		11	←	-3.6	-3.1	-3.3	-3.3
1315	ABCT membrane-spanning permease-Asp/Glu		11	←	-3.3	-3.0	-3.2	-3.3
1316	Conserved hypothetical		11	←	-3.1	-2.8		
1317	O6-methylguanine-DNA methyltransferase	<i>ogt</i>	11	←	-4.3	-3.6		
1318	Hypothetical		11	←	-3.1	-3.1		
1319	Hypothetical		11	→	-4.0	-3.2		
1320	Conserved hypothetical		11	→	-3.1		-2.7	-2.6
1321	Conserved hypothetical		11	←	-4.5	-4.0	-2.9	-3.0
1322	Pyridoxine biosynthesis	<i>pdx1</i>	11	←	-4.7	-3.9		
1323	NADH oxidase	<i>noxA</i>	11	←	-2.2	-2.7		
1335	Oxidoreductase	<i>mocA</i>			-2.5			-2.4
1336	DEAD RNA helicase				-3.0	-2.4		
1337	Degenerate transposase						3.0	3.0
1338	Degenerate transposase				3.5		3.2	3.1
1339	Degenerate transposase				3.3		2.3	2.3
1340	Degenerate transposase				4.2	3.2	2.8	2.8
1341	Degenerate transposase				5.8			
1342	Degenerate transposase						2.4	2.4
1346	Hypothetical				-3.6			
1353	ABCT substrate-binding protein-Gln	<i>glnH</i>	12	←	-3.2	-2.7		
1354	ABCT ATP-binding protein-Gln	<i>glnQ</i>	12	←	-3.0	-2.5		
1355	ABCT membrane-spanning permease-Gln	<i>glnP</i>	12	←	-2.1			
1358	Conserved hypothetical		12	→				-2.0
1359	Proton-ATPase, F1 sector, epsilon-subunit	<i>atpe</i>	12	←	-2.5	-2.6		
1360	Proton-ATPase, F1 sector, beta-subunit	<i>atpb</i>	12	←	-3.1	-3.2		
1361	Proton-ATPase, F1 sector, gamma-subunit	<i>atpg</i>	12	←	-3.2	-3.0		
1362	Proton-ATPase, F1 sector, alpha-subunit	<i>atpa</i>	12	←	-3.5	-3.4	-3.4	-3.5
1363	Proton-ATPase, F1 sector, delta-subunit	<i>atpd</i>	12	←	-4.0	-3.9	-2.9	
1364	Proton-ATPase, F0 sector, subunit b	<i>atpB</i>	12	←	-3.6	-3.2		
1365	Proton-ATPase, F0 sector, subunit a	<i>atpA</i>	12	←	-3.2	-3.1		
1366	Proton-ATPase, F0 sector, subunit c	<i>atpC</i>	12	←	-3.3	-3.0		
1367	Transposase							-2.1
1378	ABCT							2.8
1383	Polysaccharide transporter				-2.0			
1384	UDP-N-acetylmuramoyl-L-Ala-D-Glu-L-Lys ligase	<i>murE</i>			-2.1			
1386	Hypothetical				2.6	2.1		
1387	Hypothetical				2.4	2.2	2.2	2.1
1388	Hypothetical				2.3	2.0		

1389	Manganese-dependent inorganic pyrophosphatase	<i>ppaC</i>	1.9				
1390	Conserved hypothetical		2.7	2.4			
1391	Conserved hypothetical		2.3	2.1			
1392	Conserved hypothetical		2.7	2.6			
1393	Hypothetical		2.5	2.1			
1397	Asn-tRNA synthetase	<i>asnS</i>	-2.2	-2.0			
1398	Conserved hypothetical		-2.1	-2.0			
1399	Asp aminotransferase	<i>aspB</i>	-2.3	-2.0	-2.0		
1400	Conserved hypothetical		-2.6	-2.2	-2.5	-2.5	
1402	Hypothetical		4.5				
1407	Hypothetical		-2.4	-2.1			
1408	Formylmethionine deformylase	<i>def</i>	-2.9	-2.6			
1420	Hypothetical		2.6	2.4			
1430	DNA binding, peroxide resistance	<i>dpr</i>	-2.3	-2.4			
1433	Conserved hypothetical		2.5	2.0			
1434	Homoserine O-succinyltransferase	<i>metA</i>	2.4				
1435	Adenine P-ribosyltransferase	<i>apt</i>	2.0				
1436	Conserved hypothetical		3.1				
1438	Isochorismatase	<i>entB</i>	1.9				
1439	Transcriptional pleiotropic repressor	<i>codY</i>	2.0				
1440	Conserved hypothetical			-2.3			
1441	Major facilitator:Oxalate:formate antiporter	<i>oxIT</i>	8.1	3.3			
1446	Degenerate transposase (orf2)				2.0	2.0	
1447	Degenerate transposase (orf2)				2.9	2.9	
1448	Degenerate transposase (orf1)				4.1	4.3	
1452	Hypothetical				3.5	3.5	
1453	Major facilitator superfamily transporter		2.2				
1466	Hypothetical		-3.7	-3.2	-4.3	-4.1	
1470	Hypothetical		-3.4		-2.3		
1471	Hypothetical		-4.3	-2.9			
1472	Thr-tRNA synthetase 1	<i>thrS</i>	-2.5				
1477	Conserved hypothetical		2.5				
1478	Hypothetical		2.8				
1479	Conserved hypothetical		2.2				
1480	Iron-dependent transcriptional regulator	<i>marR</i>	2.2				
1481	Hypothetical		2.6			2.0	
1482	Hypothetical		3.5	2.5			
1483	Hypothetical		3.0				
1484	Hypothetical		2.0				2.0
1486	Conserved hypothetical		-2.8				
1487	GTP pyrophosphokinase	<i>relA</i>	-2.4	-2.1			
1490	Conserved hypothetical		-4.4	-2.6	-2.8	-2.7	
1491	Endopeptidase O	<i>pepO</i>	-3.7	-2.5			
1495	Thioredoxin-linked thiol peroxidase	<i>tpxD</i>		-3.3			
1501	Hypothetical					2.2	
1518	Conserved hypothetical		-2.6	-2.8			
1531	Neuraminidase B	<i>nanB</i>					-2.1
1536	Neuraminidase A	<i>nanA</i>	3.4				

1537	Hypothetical		5.5	4.2		
1539	ATP-dependent DNA helicase	recG	2.1	2.1		
1540	Ala racemase	alr	2.1	2.0		
1549	Hypothetical				-2.2	
1558	Conserved hypothetical		2.4			
1559	ABCT ATP-binding		3.6	2.4		3.3
1560	Hypothetical		5.2	3.2	4.5	4.9
1561	LPxTG protein. Sialidase A precursor	natB			2.9	2.8
1563	Degenerate transposase		3.9		3.3	3.0
1585	Conserved hypothetical				2.9	2.6
1598	Ser/Thr transporter	dctA	-3.8	-3.1	-2.3	-2.3
1599	Conserved hypothetical		-2.5	-2.0		
1602	Thioredoxin reductase	trxA	2.1			
1603	Conserved hypothetical		2.9			
1612	Conserved hypothetical		-2.4		-2.3	-2.3
1620	ABCT substrate-binding-sugar		-2.1	-2.2		
1621	Sucrose operon repressor	scrR	-2.0	-2.2		
1624	Conserved hypothetical		1.9			
1627	Conserved hypothetical				2.1	2.1
1628	Peptidase-Mtase, process CglC, CglD, CglF	cclA			7.1	6.8
1629	Conserved hypothetical		2.0		5.7	5.7
1630	Hypothetical		2.0		5.9	6.0
1631	Trp synthase alpha chain	trpA	-3.1			
1632	Trp synthase beta chain	trpB	-2.9			
1633	P-ribosylanthranilate isomerase.	trpF	-4.1			
1634	Indole-3-glycerol-P synthase	trpC	-2.9			
1635	Anthranilate P-ribosyltransferase	trpD	-4.1			
1636	Anthranilate synthase component II	trpG	-3.0			
1637	Anthranilate synthase component I	trpE	-3.4			
1638	Hypothetical		-3.8	-3.7		
1640	Hypothetical			4.1		
1654	Conserved hypothetical		-2.7	-2.1		
1655	Conserved hypothetical		-3.1	-2.3		
1656	ABCT ATP-binding/membrane spanning		-2.7	-2.2		
1657	ABCT ATP-binding/membrane spanning		-3.3	-2.6	-2.4	-2.4
1658	Conserved hypothetical		-3.0	-2.4		
1659	Hypothetical		-2.8			
1664	Restriction system	dpnD		-3.0		
1665	Type II restriction enzyme DpnI	dpnC	-3.5	-3.3	-3.0	-3.0
1666	Conserved hypothetical		-7.0	-7.5		
1672	Cation efflux system protein	czcD	16.4	7.3		
1673	Conserved hypothetical		-3.2		-2.0	
1675	Transposase		3.5			
1681	Hypothetical		-3.1			
1682	Glu aminopeptidase	pepA	-3.0	-2.5		
1698	Dextran glucosidase	dexS	-6.2	-5.3		
1699	PTS trehalose-specific IIBC component	treP	-5.8	-5.2		
1701	Degenerate transposase		3.3			3.3

1702	Degenerate transposase				3.3		2.4	2.4		
1716	Degenerate transposase				8.5	4.6				
1719	Conserved hypothetical					2.4				
1721	Degenerate transposase				5.5	3.2				
1722	Chaperonin GroEL			<i>groEL</i>			3.2			
1723	Cochaperonin GroES			<i>groES</i>	2.1					
1729	Conserved hypothetical						-3.4	-3.5		
1730	Hypothetical				-4.6	-4.5	-3.4	-3.4		
1731	Hypothetical				-5.5	-5.3	-2.8	-2.7		
1732	Conserved hypothetical				-3.6	-3.5				
1733	Hypothetical				-3.6	-3.6				
1734	ABCT ATP-binding				5.9	5.6	2.7	2.5		
1735	ABCT ATP-binding				6.5					
1736	ABCT ATP-binding				7.2	5.4	2.0			
1737	Conserved hypothetical				8.7	6.6	2.8	2.4		
1738	Conserved hypothetical				2.1	2.1				
1750	Hypothetical	5	←		3.2			2.7		
1751	Hypothetical	5	←		3.5					
1752	Hypothetical	5	←		3.3		2.1			
1753	Hypothetical	5	←		3.6					
1755	Hypothetical	5	←		1.8		5.3	5.5		
1756	DNA-damage-inducible protein			<i>dinF</i>	5	←	4.5	4.8		
1757	DNA recombination/repair			<i>recA</i>	5	←	4.3	5.0		
1758	Membrane protein			<i>cinA</i>	5	←	5.1	6.0		
1762	Hypothetical	5	←				7.4			
1763	Transcriptional activator			<i>plcR</i>	5	←	5.1	4.8	3.0	
1764	Hypothetical	5	→		13.6	14.2		3.8		
1765	Hypothetical	5	→		14.4	12.8				
1766	Hypothetical	5	→		18.9	13.9				
1767	Bacteriocin formation protein			<i>cylM</i>	5	→	26.0	15.9	5.3	5.0
1768	Conserved hypothetical	5	→		23.2	14.1				
1769	Hypothetical	5	→		21.7	13.3				
1770	ABCT ATP-binding/membrane-spanning-hemolysin			<i>cylB</i>	5	→	21.8	12.8	2.0	
1771	Subtilisin-like Ser protease			<i>nisP</i>	5	→	16.6	9.6	2.4	
1772	Hypothetical	5	→		4.6	2.9	4.9	4.9	2.0	
1773	ABCT ATP-binding	5	→		4.6	3.0				
1774	Hypothetical	5	→		5.4					
1775	Nucleoside di-P kinase			<i>ndk</i>	5	←	4.1	3.4	3.5	
1776	RNA polymerase, beta subunit			<i>rpoC</i>	5	←	2.3	2.0		
1785	Asp-ammonia ligase			<i>asnA</i>			-2.5	-2.2		
1795	Conserved hypothetical				-2.2					
1796	Conserved hypothetical				-1.9					
1797	Pentose-5-P-3-epimerase			<i>rpe</i>			-2.1			
1798	Conserved hypothetical				-2.3					
1799	Ribosomal RNA small subunit methyltransferase			<i>rsmA</i>			-2.5			
1808	Potential aminotransferase			<i>aspC</i>			-4.3	-3.5	-2.3	-2.4
1810	Conserved hypothetical				-3.1	-2.6				

1811	Conserved hypothetical			-4.3	-3.0		-3.2
1812	L-asparaginase	asnB		-3.2		-2.0	-2.1
1815	Histidine kinase				2.2		
1816	Conserved hypothetical			2.6	2.7		
1817	ABCT ATP binding			2.7	2.6	2.2	2.2
1818	Hypothetical			4.8	3.2	3.5	3.6
1819	Competence-specific transcription modulator	comX2				9.6	9.8
1826	Conserved hypothetical			2.2	2.4	3.1	
1827	Transposase			3.1	2.7		
1828	Transposase			2.0		4.0	4.3
1829	Nicotinate-nucleotide pyrophosphorylase	nadC				3.8	3.8
1830	Conserved hypothetical					3.9	3.9
1837	Alcohol-acetaldehyde DH	adhE		-7.4			
1838	Hypothetical			-3.3	-2.8	-2.8	-2.7
1839	Conserved hypothetical			-3.0	-2.7	-2.6	-2.6
1840	Conserved hypothetical			-3.1	-2.9		
1841	Transketolase	tktA		-3.9	-4.6		
1850	Hypothetical						2.1
1857	Hypothetical					17.4	16.3
1858	Membrane protein, cell wall chanel	cglG				16.1	16.2
1861	Membrane protein, cell wall chanel	cglD				13.8	14.3
1862	Membrane protein, cell wall chanel	cglC				16.9	17.4
1863	ABCT, transport of CglC-CglG	cglB				14.0	15.5
1864	ABCT, transport of CglC-CglG	cglA					9.3
1865	Conserved hypothetical			-2.4			
1866	Zinc-containing alcohol DH	adh		-2.5			
1867	N-acetylglucosamine-6-P deacetylase	nagA		-2.5		-3.8	-3.8
1868	Hypothetical			-2.1			
1869	tRNA-guanine transglycosylase	tgt		-4.1	-4.1		
1870	Hypothetical			-2.5		-2.5	-2.4
1872	Pyrrolidone carboxyl peptidase			-3.0			
1873	Conserved hypothetical						-2.1
1875	Conserved hypothetical			-2.2			
1876	Hypothetical		6	←	3.6	2.9	
1877	Multi antimicrobial extrusion family		6	←	3.7	3.1	
1878	Thr synthase	thrC	6	←	2.4	2.1	
1879	Hypothetical		6	←	3.0	2.8	2.2
1883	Hypothetical		6	←	5.4	4.9	6.4
1884	Gln amidotransferase	guaA	6	←	6.9	6.3	6.3
1885	ABCT ATP-binding-fluoroquinolones	patB	6	←	3.8	4.1	
1886	Degenerate transposase		6	→	3.2	3.8	
1887	ABCT ATP-binding-fluoroquinolones	patA	6	←	3.7	4.1	2.8
1888	DNA mismatch repair protein	hexA	6	←		2.1	
1897	ABCT membrane-spanning permease-P	pstA					2.1
1898	ABCT ATP-binding-P	pstB			2.8		2.1
1899	Negative regulator of pho regulon	phoU			3.1		2.2
1912	Hypothetical			-2.0			
1913	rRNA (guanine-N1)-methyltransferase	rrmA		-2.7			

1915	Hypothetical			-2.9	-2.4				
1918	ABCT substrate-binding-maltose	<i>malX</i>		-7.4	-5.9				
1919	ABCT membrane-spanning permease-maltose	<i>malC</i>		-4.8	-3.2				
1920	ABCT membrane-spanning permease-maltose	<i>malD</i>		-4.0					
1921	MalA protein	<i>malA</i>		-4.6	-3.4				
1922	Maltose operon transcriptional repressor	<i>malR</i>		-4.1	-3.6				
1934	Conserved hypothetical								-2.7
1935	Dihydroxyacid dehydratase	<i>ilvD</i>		-3.4	-2.2				
1936	Putative transketolase C-terminal section	<i>tktC</i>		-5.0	-4.0				
1937	Putative transketolase N-terminal section	<i>tktN</i>		-4.5	-3.7				
1938	Conserved hypothetical			-5.7	-4.5				
1939	Hypothetical			-6.4	-5.2				
1940	Conserved hypothetical			-8.7	-6.2				
1942	Hypothetical								-2.0
1945	Choline-binding protein			-5.2	-3.1				
1951	Conserved hypothetical					-2.2	-2.1		
1953	Conserved hypothetical			-4.2	-3.1				
1954	Hypothetical					-2.2			
1958	Carbamate kinase	<i>arcC</i>		2.2	2.3				
1959	Conserved hypothetical			2.9	3.1				
1960	Conserved hypothetical			2.9	3.1				
1962	Conserved hypothetical			-2.9	-3.0				
1968	PTS sugar-specific EII component					-2.3			
1971	Fucose pathway protein					-2.1	-2.0		
1972	L-fuculose P aldolase	<i>fucA</i>				-2.2	-2.2		
1979	D-Ala transfer from undecaprenol-P to the poly(glycerol-P) chain	<i>dltD</i>		-4.0	-2.6				
1980	D-Ala carrier protein	<i>dltC</i>		-3.2					
1981	D-Ala transfer from Dcp to undecaprenol-P	<i>dltB</i>		-4.5	-2.9	-3.3	-3.3		
1982	D-Ala-D-Ala carrier protein ligase	<i>dltA</i>		-4.8	-3.7				
1983	Conserved hypothetical			-2.8					
1992	Hypothetical			-3.2					
1993	Chaperonin (heat shock protein 33)	<i>hslO</i>				-2.3			
1994	Conserved hypothetical					-2.0			
2002	ABCT ATP-binding protein-anion		7	←	8.5	7.1		4.4	
2003	Conserved hypothetical		7	←	7.5	6.5	7.2	7.9	
2004	ABCT membrane-spanning permease		7	←	7.0	6.3	3.1	3.4	2.1
2005	Conserved hypothetical		7	←	7.7	6.7	6.8	6.7	2.5
2006	Choline binding protein D	<i>cbpD</i>	7	←	2.5	2.3	11.6	11.8	
2007	Conserved hypothetical		7	←	2.3	2.9			
2008	Replicative DNA helicase	<i>dnaC</i>	7	←	2.0	2.7			
2009	50S Ribosomal protein subunit L9	<i>rplI</i>	7	←	1.9	2.4			
2010	Conserved hypothetical		7	←		2.2			
2012	Involved in competence	<i>comFC</i>	7	←			11.9	11.3	
2013	Involved in competence	<i>comFA</i>	7	←			8.1	6.9	
2018	Degenerate transposase				2.9		2.1	2.1	
2021	General stress protein GSP-781					-2.0			
2022	Cell-shape determining protein MreD	<i>mreD</i>			2.5	2.2			

2023	Cell shape determining protein MreC	<i>mreC</i>			1.8		
2025	ABCT ATP-binding-unknown substrate				2.0	1.9	
2027	P-glycero-P synthase	<i>pgsA</i>			2.0	2.0	
2028	Conserved hypothetical				1.9		
2031	Conserved hypothetical				2.2	2.4	
2032	Recombination protein	<i>recF</i>			2.6	2.6	
2033	Inosine-5-mono-P DH	<i>imdH</i>			-2.1		
2036	Conserved hypothetical					2.1	
2040	Conserved hypothetical		1	→		3.3	3.2
2041	Response regulator	<i>comE</i>	1	←	2.1	23.5	23.0
2042	Histidine protein kinase	<i>comD</i>	1	←	2.0	18.9	18.9
2043	Competence stimulating peptide precursor	<i>comC</i>	1	←		6.0	6.0

^aABCT, ATP-binding cassette transporter; DH, dehydrogenase; P, phospho; PTS, phosphotransferase system.

^bDEGs included were those showing significant fold variations detected either in microarrays (≥ 2 and $P < 0.05$) or by RNASeq ($P < 1E-14$).

Table S2. Response of 35 *S. pneumoniae* R6 genes encoding DNA repair proteins

Uniprot code (_STRR6)	Description	Gene	R6 locus	SCN RESPONSE	SCN DOMAIN	Length (aa)
Q8DRQ1	Transcription-repair-coupling factor	<i>mfd</i>	spr0006	UP	UP	1,169
Q8DRP0	DNA repair protein	<i>radA</i>	spr0025	NR	NR	420
DPO1	DNA polymerase I	<i>polA</i>	spr0032	DOWN	NR	877
RECO	DNA repair protein	<i>recO</i>	spr0036	NR	NR	256
HEXB	DNA mismatch repair	<i>hexB</i>	spr0160	NR	NR	649
RUVA	Holliday junction DNA helicase	<i>ruvA</i>	spr0165	NR	NR	197
UVRA	UvrABC system protein A	<i>uvrA</i>	spr0171	NR	NR	943
RUVB	Holliday junction DNA helicase	<i>ruvB</i>	spr0238	NR	NR	332
RECU	Holliday junction resolvase	<i>recU</i>	spr0330	NR	NR	198
DPO4	DNA polymerase IV	<i>dinB</i>	spr0414	NR	NR	353
Q8CZ40	Uncharacterized protein		spr0488	NR	NR	131
Q8DQR4	Single-stranded DNA-specific exonuclease	<i>recJ</i>	spr0537	DOWN	NR	744
UVRC	UvrABC system protein C	<i>uvrC</i>	spr0543	NR	NR	614
Q8DQ41	Competence protein	<i>celA</i>	spr0856	UP	NR	216
FPG	Formamidopyrimidine-DNA glycosylase	<i>mutM</i>	spr0872	DOWN	NR	274
DNLJ	DNA ligase	<i>ligA</i>	spr1024	NR	NR	652
ADDB	ATP-dependent helicase	<i>rexB</i>	spr1039	NR	NR	1,091
ADDA	ATP-dependent helicase	<i>addA</i>	spr1040	NR	NR	1,216
MUTX	8-oxo-dGTP diphosphatase	<i>mutX</i>	spr1054	NR	NR	154
UNG	Uracil-DNA glycosylase	<i>ung</i>	spr1055	NR	NR	217
Q8DPN3	DNA repair protein	<i>recN</i>	spr1084	NR	NR	555
UVRB	UvrABC system protein B	<i>uvrB</i>	spr1118	NR	NR	662
Q8DPH8	Endonuclease III	<i>nth</i>	spr1157	NR	NR	209
Q8DP74	O6-methylguanine-DNA methyltransferase	<i>ogt</i>	spr1317	DOWN	DOWN	176
SSB	Single-stranded DNA-binding	<i>ssb</i>	spr1395	NR	NR	156
RECR	Recombination protein	<i>recR</i>	spr1516	NR	NR	198
Q7ZAK6	Branch migration of Holliday junction	<i>recG</i>	spr1539	UP	NR	671
EXOA	Exodeoxyribonuclease	<i>exoA</i>	spr1660	NR	NR	275
RECX	Regulatory protein	<i>recX</i>	spr1718	NR	NR	258
Q8DNH4	Single-stranded DNA-binding	<i>ssbB</i>	spr1724	NR	NR	131
RECA	Protein RecA	<i>recA</i>	spr1757	UP	UP	388
HEXA	DNA mismatch repair protein HexA	<i>hexA</i>	spr1888	UP	UP	844
MALX	Maltose/maltodextrin-binding protein	<i>malX</i>	spr1918	NR	NR	423
RECF	DNA replication and repair protein	<i>recF</i>	spr2032	NR	NR	365

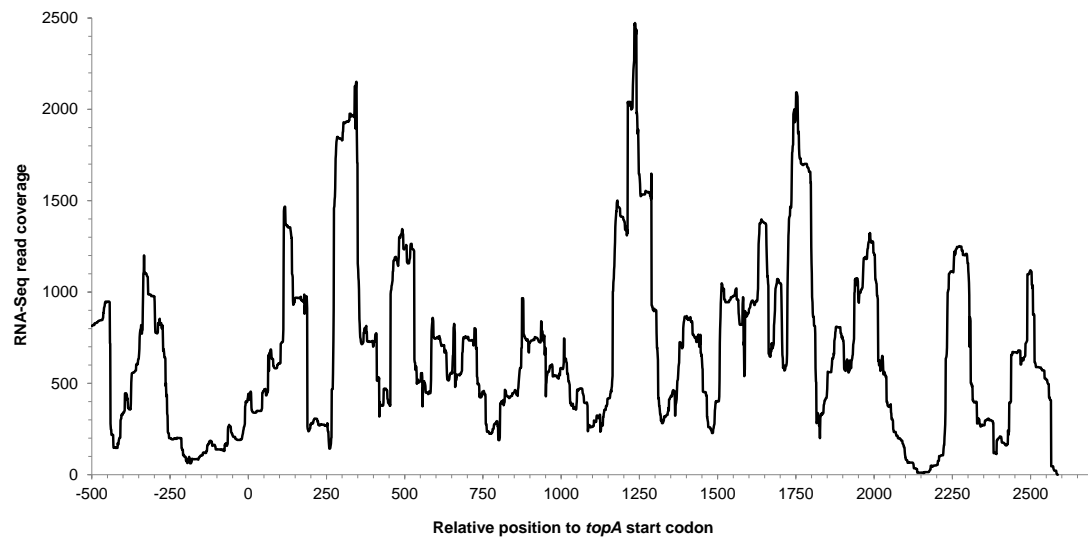


Figure S1. Determination of the start transcription site of *topA* by RNA-Seq. Thirty million reads from the RNA-Seq experiment of R6 strain grown in AGCH containing 0.2% yeast extract and 0.3% sucrose yeast extract to OD_{620nm} of 0.4 (see Methods) were considered. The total of 27,809 reads (roughly 0.1% of reads; in the range of the genome average) fully mapped within the genome section covering from -500 to +500 the *topA* ORF. The lowest read counts (<90 reads were found in the intergenic regions (~-200 and ~+2150 nt) just besides the predicted transcriptional terminators of *topA* and the preceding ORF. However, there were also prominent valleys inside the coding sequence (e.g. 143 reads, nt +260). The number of reads upstream *topA* increases just after its well-defined -35 and -10 promoter boxes, in particular from the -24 nucleotide (>190 reads). This nucleotide correspond to an “A” nucleotide, normally involved as transcription starts, surrounded by three (upstream) and two (downstream) less-probable “T” nucleotides. Therefore we propose the -24 position as the most probable start transcription site of *topA* in *S. pneumoniae* R6.