

Table S1. List of PCR primers of virulence genes used in this study.

Virulence genes					
No.	Gene	Locus_tag	Product	Primers (forward& reverse)	Amplicons size
1	tcdA	CDR20291_0584	Toxin A	F AGCTTTCGCTTTAGGCAGTG R TGGCTGGGTAAAGGTGTTGG	128
2	tcdB	CDR20291_0582	Toxin B	F GGAAGGTGGCTCAGGTCATA R GTCCATCCTGTTTCCCAAGC	201
3	Binary toxin CDT	CDR20291_2491	actin-specific ADP ribosyltransfer ase	F ATGGGAAGGACAAGCACTGT R CCTGCATAACCTGGAATAGCTG	156
4	tcdE	CDR20291_0583	Putative cell wall hydrolase protein	F AGGAGGCGTTATGAATATGACAA R TGCTACTTTTCTGATTCTCCATCT	166
5	dtxA(tcdC)	CDR20291_0585	Putative exported protein	F AGGAGGCGTTATGAATATGACAA R TGCTACTTTTCTGATT CCTCCATCT	105
6	tcdD(tcdR)	CDR20291_0581	Putative transcriptional regulator	F GCAAGAAATAACTCAGTAG R CTGTTTCTCCCTCTTCATAATG	135
7	agrB (accessory gene regulator)	CDR20291_2640	Accessory gene regulator B	F TTCCAACCCAACTAACACTTGC R CAGGAGGGTATCATGCAGACAAT	147
8	(accessory gene regulator	CDR20291_3187	Accessory gene regulator	F TCTCACTTCACTAAGAGGTTTGT R CAGTTCACAGGAGGTTATCATGC	208
9	spmA	CDR20291_3377	spore maturation protein A	F ACCATTTCAGCACCCAACA R TGGCACTCTGGATGGGGATA	176
10	fliA	CDR20291_0270	RNA polymerase sigma factor for flagellar	F AAGTGATAGAGAAGAGGAAGCTC R TGAAACACCTAGCACTTTCCC	174
Reference (Housekeeping) genes					
1	16S ribosomal RNA	1087908.1089531	16S ribosomal RNA	F GATGGACCCGCGTCTGATTA R CGTAGGAGTTTGGACCGTGT	120
2	RecA	CDR20291_1169	protein (recombinase A)	F ACTGGAGGACGTGCACTAAA R	146

				GCTTGCTTAAATGGTGGTGCT	
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Table S2 Oligonucleotides used to detect phage CDHS1 during lysogen and phage resistant strain isolation

Gene name	Primer sequences	Expected amplicon size
Holin	F 5'- GGACTAGGAGCAGTAGGGATAT-3' R 5'- CTTCTACGTCCGTTTTTCATTGC-3'	181 bp
Minor capsid	F 5'- AAGGGCTGTGCTTACTGGTG-3' F 5'- ACCATTTGCCCTGCCATTTC-3'	147 bp

Table S3 Stress markers investigated during *C. difficile* infection and phage therapy regimens in *G. mellonella*

Gene function	Number of genes	Gene name/locus tag	Reference
Growth	10	GME-string_contig704.0 GME stringcontig233.0_1 Juvenile hormone epoxid_1 Juvenile hormone epoxi_2 Juvenile hormone binding_1 Juvenile hormone esterase_1 Juvenile hormone-inducible_1 Juvenile hormone binding_3 Juvenile hormone binding_4 Juvenile hormone-esterase	[18, 51]
Infection	2	Moricin, Gloverin	
<i>Reproduction</i>	2	<i>Ecdysteroid_regulated_pr 1</i> <i>Ecdysteroid_22-kinase 1</i>	

Table S4 Table showing 20 most upregulated and downregulated genes with their products for both R20291 and ϕ CDHS1 during infection at 0 min. The ϕ CDHS1 genes are highlighted in yellow. Expression level changes considered significant if they differed at least 2-fold (\log_2 fold change) and at P value of 0.01.

No.	locus_tag/Gene	Fold Change(Infected vs. control 0 min)	Product/function
1	CDHS1_00037	654.211	Cro/C1-type transcriptional regulator
2	CDHS1_00046	564.626	hypothetical protein
3	CDHS1_00049	561.716	hypothetical protein
4	CDHS1_00040	519.891	hypothetical protein
5	CDHS1_00038	504.148	hypothetical protein
6	CDHS1_00045	495.471	hypothetical protein
7	CDHS1_00039	470.415	hypothetical protein
8	CDHS1_00047	466.066	single-stranded DNA-binding protein
9	CDHS1_00041	423.605	replication terminator-like protein
10	CDHS1_00035	325.126	DNAse/helicase
11	CDHS1_00042	273.94	hypothetical protein
12	CDHS1_00044	268.932	hypothetical protein
13	CDHS1_00028	162.17	hypothetical protein
14	CDR20291_2456	20.0979	nucleotide binding
15	CDR20291_1626	11.8031	sodium-dependent phosphate transport
16	CDR20291_2119	10.4262	sodium-dependent phosphate transport
17	CDR20291_2118	4.83674	ATP binding
18	<i>hymA</i>	4.55331	iron, sulfur cluster binding
19	CDR20291_3014	4.41467	membrane
20	<i>hymB</i>	3.81349	iron, sulfur cluster binding
21	CDR20291_1888	-6.5172	membrane,integral component of membrane
22	CDR20291_0191	-6.90089	membrane,integral component of membrane
23	CDR20291_1107	-7.41948	membrane,integral component of membrane
24	CDR20291_0318	-7.50064	metabolic process
25	CDR20291_2417	-7.84032	sequence-specific DNA binding
26	CDR20291_1334	-8.32649	conserved hypothetical protein
27	CDR20291_0949	-8.38665	membrane,integral component of membrane
28	<i>fldX</i>	-8.42604	electron carrier activity
29	CDR20291_1472	-9.33038	peptidoglycan turnover
30	CDR20291_1184	-9.88288	hypothetical protein
31	CDR20291_3277	-10.5225	membrane,integral component of membrane
32	CDR20291_0665	-11.8302	glycerophospholipid metabolic process
33	CDR20291_0317	-12.2253	regulation of transcription, DNA-templated
34	CDR20291_1265	-12.3782	drug transmembrane transport
35	CDR20291_1546	-12.6894	transporter activity
36	CDR20291_1935	-15.3289	hypothetical protein
37	CDR20291_1934	-17.6984	hypothetical protein
38	CDR20291_1751	-21.3311	membrane,integral component of membrane

39	CDR20291_1279	-21.434	membrane
40	CDR20291_1889	-28.5816	acyl-CoA metabolic process

Table S5 Table showing 20 most upregulated and downregulated genes with their products for both R20291 and ϕ CDHS1 during infection at 10 min. The ϕ CDHS1 genes are highlighted in yellow. Expression level changes considered significant if they differed at least 2-fold (\log_2 fold change) and at P value of 0.01.

No.	locus tag/Gene	FoldChange(Infected vs. control 10 min)	Product/function
1	CDHS1_00012	721.281	hypothetical protein
2	CDHS1_00047	612.555	Cro/C1-type transcriptional regulator
3	CDHS1_00037	586.981	single-stranded DNA-binding protein
4	CDHS1_00002	566.739	terminase large subunit
5	CDHS1_00041	487.13	replication terminator-like protein
6	CDHS1_00039	470.491	hypothetical protein
7	CDHS1_00042	460.395	hypothetical protein
8	CDHS1_00020	455.887	hypothetical protein
9	CDHS1_00040	454.529	hypothetical protein
10	CDHS1_00013	449.029	hypothetical protein
11	CDHS1_00011	414.62	minor capsid protein
12	CDHS1_00010	400.269	hypothetical protein
13	CDHS1_00017	386.067	tail tape measure
14	CDHS1_00044	379.648	hypothetical protein
15	CDHS1_00022	374.96	tail protein
16	CDHS1_00051	367.136	integrase
17	CDHS1_00049	365.803	hypothetical protein
18	CDHS1_00050	352.071	sigma70/sigmaF-like protein
19	CDHS1_00019	350.366	tail endopeptidase
20	CDHS1_00014	347.124	hypothetical protein
21	CDR20291_3359	-8.72486	conserved hypothetical protein
22	CDR20291_1073	-9.26481	hypothetical protein
23	CDR20291_0319	-10.3825	putative membrane protein
24	CDR20291_0364	-10.9479	putative membrane protein
25	CDR20291_0320	-11.1369	hypothetical protein
26	<i>mtIA</i>	-11.5234	mannitol-specific IIbc component
27	CDR20291_0363	-11.9947	Radical SAM-superfamily protein
28	CDR20291_2417	-12.5656	conserved hypothetical protein
29	<i>mtIR</i>	-12.6454	putative transcription antiterminator
30	CDR20291_3387	-13.2019	conserved hypothetical protein
31	<i>mtID</i>	-14.6155	mannitol-phosphate-dehydrogenase
32	CDR20291_2867	-14.9361	putative aminotransferase
33	<i>mtIF</i>	-16.1598	mannitol-specific IIa component
34	CDR20291_1750	-20.4967	binding protein
35	CDR20291_1751	-25.9699	permease protein
36	CDR20291_2418	-26.27	putative membrane protein
37	CDR20291_1889	-31.2186	putative acyl-CoA thioesterase
38	CDR20291_1938	-38.0721	permease protein
39	CDR20291_2419	-40.6191	putative aminotransferase
40	CDR20291_1752	-330.743	permease protein

Table S6 Table showing 20 most upregulated and downregulated genes with their products for both R20291 and ϕ CDHS1 during infection at 20 min. The ϕ CDHS1 genes are highlighted in yellow. Expression level changes considered significant if they differed at least 2-fold (\log_2 fold change) and at P value of <0.01 .

No.	locus_tag/Gene	FoldChange(Infected vs. control 20 min)	Product/function
1	CDHS1_00023	722.602	holin
2	CDHS1_00019	711.131	Distal tail protein
3	CDHS1_00025	546.103	Endolysin
4	CDHS1_00031	510.54	Hypothetical protein
5	CDHS1_00021	505.268	tail fiber protein
6	CDHS1_00002	489.217	terminase large subunit
7	CDHS1_00020	472.23	Hypothetical protein
8	CDHS1_00032	442.065	DNA-binding protein
9	CDHS1_00005	436.93	Hypothetical protein
10	CDHS1_00042	397.429	Hypothetical protein
11	CDHS1_00028	391.181	Hypothetical protein
12	CDHS1_00022	385.525	tail fiber protein
13	CDHS1_00013	381.488	Hypothetical protein
14	CDHS1_00050	380.02	sigma70/sigmaF-like protein
15	CDHS1_00007	375.468	scaffolding protein
16	CDHS1_00010	371.915	Hypothetical protein
17	CDHS1_00051	366.062	integrase
18	CDHS1_00018	359.421	tail protein
19	CDHS1_00040	349.339	Hypothetical protein
20	CDHS1_00011	347.509	minor capsid protein
21	CDR20291_2050	-8.76834	putative transcriptional regulator
22	CDR20291_0203	-9.28835	conserved hypothetical protein
23	CDR20291_2416	-9.32831	conserved hypothetical protein
24	CDR20291_1107	-9.46141	permease protein
25	CDR20291_1546	-10.5254	permease protein
26	CDR20291_2867	-10.814	putative aminotransferase
27	CDR20291_1575	-12.3802	putative membrane protein
28	CDR20291_1889	-15.2629	putative acyl-CoA thioesterase
29	CDR20291_1184	-16.1539	hypothetical protein
30	CDR20291_0319	-16.7031	putative membrane protein
31	CDR20291_0364	-21.0257	putative membrane protein
32	CDR20291_0363	-24.3725	Radical SAM protein
33	CDR20291_3194	-27.576	putative glycosyl transferase
34	CDR20291_2417	-31.4166	conserved hypothetical protein
35	CDR20291_3154	-43.4484	hypothetical protein
36	CDR20291_1751	-49.3662	permease protein
37	CDR20291_0979	-63.5015	hypothetical protein
38	CDR20291_1752	-63.7285	permease protein
39	CDR20291_2419	-82.2712	putative aminotransferase
40	CDR20291_2418	-83.2952	putative membrane protein

Table S7 Table showing 20 most upregulated and downregulated genes with their products for both R20291 and ϕ CDHS1 during infection at 30 min. The ϕ CDHS1 genes are highlighted in yellow. Expression level changes considered significant if they differed at least 2-fold (\log_2 fold change) and at P value of 0.01.

No.	locus_tag/Gene	FoldChange(Infected vs. control 30 min)	Product/function
1	ICDHS1_00032	1318.59	DNA-binding protein
2	CDHS1_00025	980.483	Endolysin
3	CDHS1_00023	979.053	holin
4	CDHS1_00001	866.272	terminase small subunit
5	CDHS1_00045	834.868	hypothetical protein
6	CDHS1_00013	823.313	hypothetical protein
7	CDHS1_00012	781.766	hypothetical protein
8	CDHS1_00031	779.161	Hypothetical protein
9	CDHS1_00002	723.079	terminase large subunit
10	CDHS1_00050	669.938	sigma70/sigmaF-like protein
11	CDHS1_00007	641.889	scaffolding protein
12	CDHS1_00040	637.818	Hypothetical protein
13	CDHS1_00010	625.585	Hypothetical protein
14	CDHS1_00021	622.64	tail fiber protein
15	CDHS1_00011	600.556	minor capsid protein
16	CDHS1_00019	592.162	Distal tail protein
17	CDHS1_00018	574.821	tail protein
18	CDHS1_00020	555.707	Hypothetical protein
19	CDHS1_00014	517.953	Hypothetical protein
20	CDHS1_00051	512.887	integrase
21	CDR20291_2104	-7.30782	putative subunit of oxidoreductase
22	CDR20291_0203	-7.49629	conserved hypothetical pr.
23	CDR20291_1753	-8.36869	utative uncharacterized pr.
24	<i>fhuB</i>	-8.46628	permease protein
25	CDR20291_2867	-8.84382	putative aminotransferase
26	CDR20291_1752	-9.35524	permease protein
27	CDR20291_1750	-9.89837	atp-binding protein
28	CDR20291_1691	-10.1105	nitrite and sulfite reductase subunit
29	CDR20291_2416	-11.062	conserved hypothetical protein
30	CDR20291_1889	-12.5392	putative acyl-CoA thioesterase
31	CDR20291_0979	-13.6647	hypothetical protein
32	CDR20291_1692	-15.8439	pyridine n-disulfide oxidoreductase
33	CDR20291_1546	-17.0769	permease protein
34	CDR20291_1334	-17.2296	conserved hypothetical protein
35	CDR20291_1751	-21.1816	permease protein
36	CDR20291_0364	-24.3586	putative membrane protein
37	CDR20291_0363	-26.0195	Radical SAM-superfamily protein

38	CDR20291_2417	-33.6534	conserved hypothetical protein
39	CDR20291_2419	-81.7977	putative aminotransferase
40	CDR20291_2418	-83.178	putative membrane protein

Table S8 Table showing 20 most upregulated and downregulated genes with their products for both R20291 and ϕ CDHS1 during infection at 40 min. The ϕ CDHS1 genes are highlighted in yellow. Expression level changes considered significant if they differed at least 2-fold (\log_2 fold change) and at *P* value of 0.01.

No.	locus_tag/Gene	Fold Change (Infected vs. control 40 min)	Product/function
1	CDHS1_00005	1091.17	hypothetical protein
2	CDHS1_00010	1076.3	Hypothetical protein
3	CDHS1_00025	957.978	Endolysin
4	CDHS1_00021	818.306	tail fiber protein
5	CDHS1_00004	799.91	minor capsid protein
6	CDHS1_00013	789.05	hypothetical protein
7	CDHS1_00023	770.38	holin
8	CDHS1_00019	768.284	Distal tail protein
9	CDHS1_00007	752.144	scaffolding protein
10	CDHS1_00001	726.61	terminase small subunit
11	CDHS1_00012	721.443	hypothetical protein
12	CDHS1_00017	710.088	tail tape measure
13	CDHS1_00014	680.081	Hypothetical protein
14	CDHS1_00011	655.499	minor capsid protein
15	CDHS1_00018	646.67	tail protein
16	CDHS1_00020	640.583	Hypothetical protein
17	CDHS1_00024	627.541	acetylmuramoyl-alanine amidase
18	CDHS1_00051	619.045	integrase
19	CDHS1_00022	598.937	tail protein
20	CDHS1_00002	587.468	terminase large subunit
21	CDR20291_1546	-5.76995	permease protein
22	CDR20291_1888	-6.06205	putative membrane protein
23	CDR20291_2905	-6.36114	glycosyl hydrolase
24	CDR20291_0020	-7.22069	transcriptional regulator
25	CDR20291_0724	-7.74541	putative membrane protein
26	CDR20291_2532	-7.87691	sporulation sigma E factor peptidase
27	CDR20291_1750	-8.78868	putative lantibiotic abc transporter
28	CDR20291_0300	-9.78877	putative biotin synthase
29	CDR20291_3277	-10.3145	putative exported protein
30	CDR20291_1889	-12.0696	putative acyl-CoA thioesterase
31	CDR20291_2417	-14.9121	conserved hypothetical protein
32	CDR20291_1752	-16.4006	permease protein
33	CDR20291_1691	-19.8677	nitrite and sulfite reductase subunit
34	CDR20291_0364	-20.8629	putative membrane protein
35	CDR20291_0363	-21.1467	Radical SAM-superfamily protein
36	CDR20291_1692	-25.4408	pyridine n-disulfide oxidoreductase

37	CDR20291_0728	-28.1149	hydroxymethylglutaryl-CoA lyase
38	CDR20291_2418	-40.4521	putative membrane protein
39	CDR20291_2419	-42.8241	putative aminotransferase
40	CDR20291_1751	-137.447	permease protein

Table S9 Table showing 20 most upregulated and downregulated genes with their products for both R20291 and ϕ CDHS1 during infection at 50 min. The ϕ CDHS1 genes are highlighted in yellow. Expression level changes considered significant if they differed at least 2-fold (\log_2 fold change) and at P value of 0.01.

No.	locus_tag/Gene	Fold Change (Infected vs. control 50 min)	Product/function
1	CDHS1_00021	1343.49	tail fiber protein
2	CDHS1_00025	1144.53	Endolysin
3	CDHS1_00011	971.929	minor capsid protein
4	CDHS1_00001	921.066	terminase small subunit
5	CDHS1_00022	907.514	tail protein
6	CDHS1_00007	885.546	scaffolding protein
7	CDHS1_00023	852.48	holin
8	CDHS1_00012	848.368	hypothetical protein
9	CDHS1_00013	818.554	hypothetical protein
10	CDHS1_00050	815.101	sigma70/sigmaF-like protein
11	CDHS1_00024	783.44	putative endolysin
12	CDHS1_00010	777.711	Hypothetical protein
13	CDHS1_00019	775.422	Distal tail protein
14	CDHS1_00002	750.84	terminase large subunit
15	CDHS1_00051	717.438	integrase
16	CDHS1_00020	620.057	Hypothetical protein
17	CDHS1_00018	618.126	tail protein
18	CDHS1_00017	616.396	tail tape measure
19	CDHS1_00015	592.191	Hypothetical protein
20	CDHS1_00014	585.389	Hypothetical protein
21	CDR20291_0602	-6.11481	putative membrane protein precursor
22	<i>fhuG</i>	-6.3018	permease protein
23	<i>fhuB</i>	-7.49698	permease protein
24	CDR20291_1750	-7.53438	atp-binding protein
25	CDR20291_1744	-7.58244	ite-specific recombinase
26	CDR20291_0203	-8.29159	conserved hypothetical protein
27	CDR20291_0319	-9.43268	putative membrane protein
28	CDR20291_1889	-9.62194	putative acyl-CoA thioesterase
29	CDR20291_2417	-10.2041	conserved hypothetical protein
30	CDR20291_3207	-10.5323	permease protein
31	CDR20291_2419	-11.8593	putative aminotransferase
32	CDR20291_2497	-12.195	conserved hypothetical protein
33	CDR20291_0364	-12.3357	putative membrane protein
34	CDR20291_2867	-12.4293	putative aminotransferase
35	CDR20291_0363	-13.4737	Radical SAM-superfamily protein
36	CDR20291_1546	-13.7981	permease protein
37	CDR20291_2418	-14.4336	putative membrane protein

38	CDR20291_1751	-22.587	permease protein
39	CDR20291_1691	-26.8781	nitrite and sulfite reductase subunit
40	CDR20291_1692	-28.5576	pyridine n-disulfide oxidoreductase