

	<b>couples</b>	<b>bad bugs</b>	<b>controls</b>
<b>1</b>	M. leprae/M. avium	26	68
<b>2</b>	M. tuberculosis/M. smegmatis	60	28
<b>3</b>	R. prowazekii/R. africae	21	3
<b>4</b>	C. diphtheriae/C. glutamicum	31	49
<b>5</b>	T. pallidum/T. denticola	19	34
<b>6</b>	Y. pestis/Y .pseudotuberculosis	179	192
<b>7</b>	B. pertussis/B. bonchiseptica	117	158
<b>8</b>	S. pneumoniae/S. agalactiae	44	47
<b>9</b>	S. pyogenes/S. suis	38	72
<b>10</b>	S. Typhi/S. Schwarzengrund	186	35
<b>11</b>	S. dysenteriae/E. coli HS	157	205
<b>12</b>	V. cholerae/V. parahaemolyticus	131	202

**Table S1. Number of “virulence factors” in the 12 pairs assessed in this study.**

<b>Bacteria</b>	<b>Genes encoding eukaryotic-like motifs</b>
<i>M. leprae</i>	<b>1 U-box domain</b> (Q9CC35_MYCLE)
<i>M. avium</i>	<b>1 U-box domain</b> (A0QKC2_MYCA1)
<i>M. tuberculosis</i>	<b>1 U-box domain</b> (O05898_MYCTU)
<i>M. smegmatis</i>	<b>2 TPR</b> (A0QT13_MYCS2, A0QY89_MYCS2) <b>1 ANK</b> (MSMEG_1266) <b>2 U-box domain</b> (A0QTG8_MYCS2, Q8KRQ4_MYCSM)
<i>R. prowazekii</i>	<b>1 TPR</b> (RT0587) <b>3 ANK</b> (RP226, RP714, RP716)
<i>R. africae</i>	<b>8 ANK</b> (raf_ORF0213, raf_ORF0264, raf_ORF0286, raf_ORF0482, raf_ORF0702, raf_ORF0782, raf_ORF0795, raf_ORF0860)
<i>C. diphtheriae</i>	<b>1 ANK</b> (Q6NFW8_CORDI) <b>1 U-box domain</b> (Q6NI57_CORDI)
<i>C. glutamicum</i>	<b>7 ANK</b> (A4QFC2_CORGB, A4QG66_CORGB, A4QHW9_CORGB, Q8NLM6_CORGL, Q8NN64_CORGL, Q8NNX2_CORGL, UP10000165DE3) <b>2 U-box domain</b> (A4QC82_CORGB, Q8N5C8_CORGL)
<i>T. pallidum</i>	<b>13 TPR</b> (007895_TREPA, 083106_TREPA, Y095_TREPA, 083292_TREPA, 083473_TREPA, 083481_TREPA, 083482_TREPA, 083484_TREPA, 083654_TREPA, 083885_TREPA, Y920_TREPA, 083920_TREPA, 083955_TREPA) <b>2 ANK</b> (Y502_TREPA, 083807_TREPA)
<i>T. denticola</i>	<b>27 TPR</b> (Q73JA3_TREDE, Q73K35_TREDE, Q73KC1_TREDE, Q73KY9_TREDE, Q73KZ24_TREDE, Q73L42_TREDE, Q73LH6_TREDE, Q73M01_TREDE, Q73M24_TREDE, Q73MH2_TREDE, Q73N08_TREDE, Q73N69_TREDE, Q73N91_TREDE, Q73ND5_TREDE, Q73NB1_TREDE, Q73NM5_TREDE, Q73NM6_TREDE, Q73NM7_TREDE, Q73NR0_TREDE, Q73P07_TREDE, Q73Q63_TREDE, Q73QJ6_TREDE, Q73QL1_TREDE, Q73QL3_TREDE, Q73QL5_TREDE, Q73R78_TREDE, Q73RP2_TREDE) <b>6 ANK</b> (TDE_2138, TDE_2450, TDE_0520, TDE_0552, TDE_2014, TDE_2693) <b>2 LRR</b> (Q733KG0_TREDE, Q73Q69_TREDE)
<i>Y. pestis</i>	<b>3 TPR</b> (A4TMT9_YERPP, Q7CIL3_YERPP, UP100006DD404) <b>1 ANK</b> (Q1CKF5_YERPN) <b>14 LRR</b> (A9ZCK3_YERPE, A9ZET9_YERPE, B0A1ZA_YERPE, YOPM_YERPE, Q7CGM7_YERPE, Q7CGM8_YERPE, Q8D0X0_YERPE, B0A3R7_YERPE, BOGK22_YERPE, B0GQ67_YERPE, BOGY75_YERPE, C4GZK9_YERPE, C4GZK7_YERPE, C4H8R8_YERPE, C4HB68_YERPE) <b>6 U-box domain</b> (A9Z9F7_YERPE, BOA2L5_YERPE, BOGR75_YERPE, C4H6C9_YERPE, C4HPN9_YERPE, Q8D0I3_YERPE)
<i>Y. pseudotuberculosis</i>	<b>2 TPR</b> (A7FFY7_YERPS, A7FI12_YERPS) <b>1 ANK</b> (A7FFS8_YERPS) <b>5 LRR</b> (A7FEI9_YERPS, A7FEJ0_YERPS, Q663L9_YERPS, Q666F7_YERPS, Q668J8_YERPS) <b>1 U-box domain</b> (Q66AE5_YERPS)
<i>B. pertussis</i>	<b>4 TPR</b> (Q7VUG8_BORPE, Q7VW81_BORPE, Q7VXV8_BORPE, Q84CS6_BORPE)
<i>B. bronchiseptica</i>	<b>3 TPR</b> (Q7WD77_BORBP, Q7WIB7_BORBP, Q7WNY7_BORBP)
<i>S. pneumoniae</i>	<b>9 U-box domain</b> (5LDY6_STRPN, A5LP58_STRPN, A5LRZ2_STRPN, A5LZU4_STRPN, A5M9I5_STRPN, A5MI31_STRPN, A5MKB3_STRPN, A5MUL9_STRPN, Q97RR1_STRPN)
<i>S. agalactiae</i>	<b>1 LRR</b> (Q2Q1G9_STRAG)
<i>S. pyogenes</i>	<b>1 LRR</b> (B0LFQ8_STRPY) <b>1 U-box domain</b> (B5I24_STRPZ)
<i>S. suis</i>	<b>2 TPR</b> (A4WZS4_STRSU, Q302B7_STRSU) <b>1 LRR</b> (B9WUM5_STRSU) <b>1 U-box domain</b> (B9WVB0_STRSU)
<i>S. Typhi</i>	<b>1 LRR</b> (Q8Z578_SALTI) <b>1 U-box domain</b> (Q8Z6R4_SALTI)
<i>S. Schwarzengrund</i>	<b>1 LRR</b> (B4TQU4_SALSV)

	<b>1 U-box domain</b> (B4TVD2_SALSV)
<i>S. dysenteriae</i>	<b>5 TPR</b> (Q32BHO_SHIDS, Q32D24_SHIDS, Q32GQ3_SHIDS, UP1000006733E4, UP1000006735E5) <b>2 LRR</b> (B3X564_SHIDY, B3X6G1_SHIDY) <b>1 U-box domain</b> (B3WXW5_SHIDY)
<i>E. coli</i>	<b>1 ANK</b> (EcHS_A0379) <b>1 LRR</b> (A8A027_ECOHS) <b>1 U-box domain</b> (A8A0F5_ECOHS)
<i>V. cholerae</i>	<b>30 TPR</b> (A1EPE8_VIBCH, A1EPE8_VIBCH, A1EPJ0_VIBCH, A1F7D2_VIBCH, A2P4M4_VIBCH, A2PT69_VIBCH, A2PXG5_VIBCH, A3EJ42_VIBCH, A3ENS9_VIBCH, A3GP76_VIBCH, A3GWT1_VIBCH, A5F321_VIBCH, A5F914_VIBCH, A6A1L5_VIBCH, A6A6N0_VIBCH, A6AGX6_VIBCH, A6AJE1_VIBCH, A6XV93_VIBCH, A6XWT3_VIBCH, A6XZM1_VIBCH, A6Y2A2_VIBCH, A6Y2F5_VIBCH, A6Y2L7_VIBCH, A6Y462_VIBCH, Q9KQT6_VIBCH, Q9KRM4_VIBCH, Q9KS92_VIBCH, Q9KTK1_VIBCH, UP1000005F2FE2, UP1000005F3140, UP1000005F316F) <b>4 ANK</b> (A1EPN6_VIBCH, A3EK26_VIBCH, Q9KRQ2_VIBCH, UP1000005F3B34)
<i>V. parahaemolyticus</i>	<b>18 TPR</b> (A6AXV6_VIBPA, A6AY66_VIBPA, A6AYK2_VIBPA, A6AZK5_VIBPA, A6B0N7_VIBPA, A6B2L2_VIBPA, A6B3T8_VIBPA, A6AXV6_VIBPA, A6B581_VIBPA, A6B8A9_VIBPA, A6B8G3_VIBPA, A6BBA0_VIBPA, Q84157_VIBPA, Q87H96_VIBPA, Q87LB0_VIBPA, Q87M07_VIBPA, Q87N48_VIBPA, Q87P81_VIBPA) <b>2 ANK</b> (A6B0E4_VIBPA, Q87JE7_VIBPA) <b>3 LRR</b> (A6B2C9_VIBPA, B8K3H5_VIBPA, Q87N90_VIBPA) <b>5 U-box domain</b> (A6AX68_VIBPA, A6AZR3_VIBPA, B3IUU9_VIBPA, Q87G92_VIBPA, Q87HJ6_VIBPA)

**Table S2. Number of genes encoding eukaryotic-like motifs in bacterial species.**

TPR: tetratricopeptide repeats, ANK: ankyrin repeats, LRR: leucine-rich repeats

<b>Bacteria</b>	<b>Number of protein secretion systems</b>
M. leprae	NO
M. avium	<b>1 type II/IV secretion protein (COG4962u)</b> <b>1 type II secretion system protein F (COG4965U)</b>
M. tuberculosis	NO
M. smegmatis	<b>2 type II secretion system protein F (MSMEG_6167, MSMEG_6168)</b> <b>1 type I secretion system protein (MSMEG_6169)</b>
R. prowazekii	<b>2 type IV secretion system ATPase (RP103, RP292)</b>
R. africae	<b>1 type I secretion outer membrane protein (raf_ORF0284)</b> <b>8 type IV secretion system ATPase (raf_ORF0128, raf_ORF0129, raf_ORF0130, raf_ORF0133, raf_ORF0134, raf_ORF0135, DQ821909.1, CP001612.1)</b>
C. diphtheriae	NO
C. glutamicum	NO
T. pallidum	NO
T. denticola	NO
Y. pestis	<b>7 type III secretion system component (y0515, y0516, y0517, y0518, y0524, y0531, y0532)</b> <b>2 type III secretion system protein (y0529, y0530)</b> <b>1 type III secretion system ATPase (y0526)</b> <b>1 type III secretion apparatus protein (y0527)</b>
Y. pseudotuberculosis	<b>4 type III secretion system protein (YPTB0312, YPTB0313, YPTB0326, YPTB0327)</b> <b>7 type III secretion system apparatus (YPTB0316, YPTB0317, YPTB0318, YPTB0321, YPTB0324, YPTB0328, YPTB0329)</b> <b>1 type III secretion system lipoprotein (YPTB0319)</b> <b>1 type III secretion system ATPase (YPTB0323)</b> <b>1 type IV secretion ATPase (YPTB3375)</b>
B. pertussis	<b>1 type II secretion system protein (BP1996)</b> <b>12 type III secretion system protein (BP2235, BP2237, BP2238, BP2239, BP2240, BP2241, BP2244, BP2246, BP2248, BP2249, BP2262, BP2264)</b> <b>1 type III secretion system ATPase (BP2245)</b> <b>1 type III secretion pore protein (BP2261)</b>
B. bronchiseptica	<b>7 type II secretion system protein (BB0780, BB0781, BB0782, BB0784, BB0790, BB1826, BB1828)</b> <b>12 type III secretion system protein (BB1609, BB1611, BB1624, BB1625, BB1627, BB1629, BB1631, BB1632, BB1633, BB1634, BB1635, BB1637)</b> <b>1 type III secretion system ATPase (BB1628)</b>
S. pneumoniae	NO
S. agalactiae	NO
S. pyogenes	NO
S. suis	NO
S. Typhi	<b>5 type I secretion system protein (STY2876, STY2878, STY4456, STY4457, STY4460)</b> <b>1 type I secretion system protein, ATP-binding (STY2877)</b> <b>1 type II secretion system protein (STY3252)</b> <b>3 type III secretion system protein (STY1699, STY1700, STY1701, STY1702, STY1703, STY1704)</b> <b>1 type III secretion system ATPase (STY1705)</b> <b>1 type III secretion system chaperone protein (STY1721)</b>
S. Schwarzengrund	<b>3 type I secretion system protein (SeSA_A2887, SeSA_A2889, SeSA_A4513)</b> <b>2 type III secretion outer membrane pore (SeSA_A1491, SeSA_A3051)</b> <b>7 type III secretion apparatus protein (SeSA_A1492, SeSA_A1504, SeSA_A1507, SeSA_A3041, SeSA_A1517, SeSA_A3027, SeSA_A3023)</b> <b>4 type III secretion system protein (SeSA_A1493, SeSA_A1503, SeSA_A1514, SeSA_A1515)</b> <b>3 type III secretion system low calcium response chaperone (SeSA_A1495, SeSA_A1499, SeSA_A3039)</b> <b>2 type III secretion apparatus needle protein (SeSA_A1502, SeSA_A3026)</b>

	<b>2 type III secretion system apparatus lipoprotein</b> (SeSA_A1505, SeSA_A3024) <b>1 type III secretion system ATPase</b> (SeSA_A1511) <b>6 type IV secretion system protein</b> (SeSA_A0297, SeSA_A0298, SeSA_A0305, SeSA_A0306, SeSA_A0313, SeSA_A0318) <b>1 type secretion system lysozyme-related protein</b> (SeSA_A0299) <b>1 type IV secretion system ATPase</b> (SeSA_A0303) <b>1 type IV secretion system lipoprotein</b> (SeSA_A0312)
<i>S. dysenteriae</i>	<b>9 type II secretion system protein</b> (SDY_3092, SDY_3093, SDY_3094, SDY_3095, SDY_3096, SDY_3097, SDY_3098, SDY_3099, SDY_3100)
<i>E. coli</i>	<b>2 type III secretion system apparatus</b> (EcHS_A3009, EcHS_A3011) <b>1 type III secretion system needle protein</b> (EcHS_A3010) <b>1 type IV secretion system protein</b> (EcHS_A0616)
<i>V. cholerae</i>	NO
<i>V. parahaemolyticus</i>	<b>14 type III secretion system protein</b> (VP1664, VP1665, VP1669, VP1671, VP1672, VP1688, VP1689, VP1693, VP1696, VPA1339, VPA1342, VPA1349, VPA1354, VPA1355) <b>1 type III secretion system ATPase</b> (VP1668) <b>2 type III secretion system lipoprotein</b> (VP1690, VPA1367) <b>1 type III secretion apparatus</b> (VPA1335)

**Table S3. Number of secretion system proteins in bacterial species.**

<b>Bacteria</b>	<b>position of IS</b>	<b>size of IS (bp)</b>	<b>number of operons</b>	<b>of which split</b>
M. leprae	no IS		1	0
M. avium	no IS		1	0
M. tuberculosis	no IS		1	0
M. smegmatis	no IS		2	0
R. prowazekii	no IS		1	1
R. africae	no IS		1	1
C. diphtheriae	5229-5250 *	21	5	0
C. glutamicum	no IS		6	0
T. pallidum	no IS #		2	2
T. denticola	1876-1903	27	2	2
	4981-5008	27		
Y. pestis	1651-1690 *	49	7	7
Y. pseudotuberculosis	no IS		7	7
B. pertussis	no IS		3	3
B. bronchiseptica	no IS		3	3
S. pneumoniae	no IS		4	4
S. agalactiae	no IS		7	7
S. pyogenes	5265-5297 *	32	6	6
S. suis	no IS		5	5
S. Typhi	2679-2713 #	34	7	7
	2723-2788 #	65		
	3781-3802 #	27		
	5317-5340 #	23		
	5371-5400 #	29		
S. Schwarzengrund	1722-1735	15	3	3
	1763-1785	22		
	1804-1814	10		
	1832-1849	17		
	1880-1895	15		
	1962-1974	12		
S. dysenteriae	no IS #		7	7
E. coli HS	3121-3143	22	7	7
	3165-3180	15		
V. cholerae	1591-1668 *	77	8	8
V. parahaemolyticus	no IS		10	10

**Table S4. Position and size of IVSs in the evaluated bacterial species.**

\*: “bad bugs” with one likely IVS, #: “bad bugs” with fewer IVSs compared to their controls

	<b>Bacteria</b>	<b>Number of Tandem repeats</b>	<b>Size (pb)</b>
<b>1</b>	<i>M. leprae</i>	144	2-30
	<i>M. avium</i>	561	6-246
<b>2</b>	<i>M. tuberculosis</i>	565	3-257
	<i>M. smegmatis</i>	192	6-231
<b>3</b>	<i>C. diphtheriae</i>	75	9-411
	<i>C. glutamicum</i>	92	8-390
<b>4</b>	<i>T. pallidum</i>	12	9-96
	<i>T. denticola</i>	82	2-198
<b>5</b>	<i>Y. pestis</i>	559	4-477
	<i>Y. pseudotuberculosis</i>	934	5-496
	plasmid 1	6	7-246
	plasmid 2	5	8-78
	chromosome	923	5-496
<b>6</b>	<i>B. pertussis</i>	233	6-270
	<i>B. bronchiseptica</i>	233	6-270
<b>7</b>	<i>S. pneumoniae</i> *	71	6-213
	<i>S. agalactiae</i>	67	9-293
<b>8</b>	<i>S. pyogenes</i> *	42	9-243
	<i>S. suis</i>	16	10-255
<b>9</b>	<i>S. Typhi</i> *	94	3-273
	plasmid 1	11	3-273
	plasmid 2	2	15-162
	chromosome	83	12-21
	<i>S. Schwarzengrund</i>	83	3-273
	plasmid 1	3	3-300
	plasmid 2	0	43-106
chromosome	80	3-300	
<b>10</b>	<i>S. dysenteriae</i> *	18	8-297
	Plasmid 1	1	9
	Plasmid 2	1	21
	chromosome	16	8-297
	<i>E. coli</i>	30	14-380
<b>11</b>	<i>V. cholerae</i> *	84	6-438
	chromosome 1	36	6-438
	chromosome 2	48	6-414
	<i>V. parahaemolyticus</i>	81	6-480
	chromosome 1	58	6-480
	chromosome 2	23	6-429

**Table S5. Number and size of tandem repeat sequences in bacteria.**

\*: “bad bugs” carrying more tandem repeat sequences compared to their controls

<b>Bacteria</b>	<b>Small RNAs Accession</b>	<b>Number of sRNAs</b>
<i>M. leprae</i>	RF00380, RF00515, RF00379	<b>3</b>
<i>M. avium</i>	RF00379, RF00380, RF00442, RF00515	<b>4</b>
<i>M. tuberculosis</i>	RF00080, RF00379, RF00380, RF00515	<b>4</b>
<i>M. smegmatis</i>	-	<b>0</b>
<i>R. prowazekii</i>	-	<b>0</b>
<i>R. africae</i>	-	<b>0</b>
<i>C. diphtheriae</i>	RF00080	<b>1</b>
<i>C. glutamicum</i>	RF00080, RF00379	<b>2</b>
<i>T. pallidum</i>	-	<b>0</b>
<i>T. denticola</i>	-	<b>0</b>
<i>Y. pestis</i>	RF00018,RF00021,RF00034, <b>2</b> RF00057,RF00078, RF00079,RF00081, RF00082,RF00101,RF00110, RF00111,RF00112,RF00127, RF00128,RF00369,RF01339, <b>2</b> RF01396, <b>19</b> RF01405	<b>37</b>
<i>Y. pseudotuberculosis</i>	RF00018, RF00021, RF00034, RF00057, RF00078, RF00079, RF00081, RF00082, RF00110, RF00111, RF00112, RF00127, RF00128, RF00368, RF00369, RF01394, RF01396, <b>2</b> RF01405,	<b>19</b>
<i>B. pertussis</i>	RF00140, RF01070	<b>2</b>
<i>B. bronchiseptica</i>	RF00140, RF00624, RF01068, RF01070	<b>4</b>
<i>S. pneumoniae</i>	RF00230, RF00515	<b>2</b>
<i>S. agalactiae</i>	RF00029, RF00235	<b>2</b>
<i>S. pyogenes</i>	RF00029, RF00235	<b>2</b>
<i>S. suis</i>	Listeria snRNA rli28	<b>1</b>
<i>S. Typhi</i>	RF00014, RF00018, RF00021, RF00034, RF00035, <b>2</b> RF00057, RF00077, RF00078, RF00079, RF00081, RF00082, RF00084, RF00101, RF00110, RF00111, RF00112, <b>3</b> RF00113, RF00118, RF00120, RF00121, RF00124, RF00126, RF00127, <b>2</b> RF00128, RF00368, RF00369, RF00370, RF00505, RF01388, RF01390, RF01391, RF01394, RF01397, RF01398, RF01399, RF01401, RF01402, RF01403, RF01404, <b>18</b> RF01405, RF01406, RF01407, RF01409	<b>64</b>



S. Schwarzengrund	RF00018, RF00021, RF00035, <b>2</b> RF00057, RF00077, RF00078, RF00081, RF00101, RF00110, RF00111, RF00112, <b>3</b> RF00113, RF00118, RF00126, RF00127, <b>2</b> RF00128, RF00369, RF00370, RF00505, RF01388, RF01390, RF01391, RF01393, <b>2</b> RF01396, RF01397, RF01398, RF01399, RF01401, RF01402, RF01403, RF01404, RF01406, RF01407, RF01409	<b>39</b>
S. dysenteriae	RF00014, RF00018, RF00021, RF00034, RF00035, RF00057, RF00079, RF00082, RF00084, RF00101, RF00110, RF00111, RF00115, RF00116, RF00117, RF00118, RF00119, RF00120, RF00121, RF00124, RF00126, RF00368, RF00369, RF00370, RF00372, RF01394, RF01405, RF01407	<b>28</b>
E. coli	RF00014, RF00018, RF00034, <b>6</b> RF00035, <b>2</b> RF00077, RF00078, RF00082, RF00101, RF00112, RF00113, RF00115, RF00116, RF00117, RF00119, RF00125, RF00126, RF00127, RF00128, RF00368, RF00369, RF00370, RF00372, RF00505	<b>29</b>
V. cholerae	<b>2</b> RF00018, RF00021, RF00057, RF00111, RF00368, <b>4</b> RF00378, RF01394	<b>11</b>
V. parahaemolyticus	<b>2</b> RF00018, RF00021, RF00057, RF00111, RF00127, RF00368, <b>5</b> RF00378	<b>12</b>

**Table S6. Number of sRNAs in “bad bugs” and in controls.**

<b>Bacteria</b>	<b>Number of TA systems</b>
M. leprae	0
M. avium	1
M. tuberculosis *	38
M. smegmatis	0
R. prowazekii	0
R. africae	10
C. diphtheriae	0
C. glutamicum	1
T. pallidum	0
T. denticola	1
Y. pestis *	5
Y. pseudotuberculosis	0
B. pertussis	0
B. bronchiseptica	0
S. pneumoniae *	5
S. agalactiae	2
S. pyogenes *	2
S. suis	0
S. Typhi *	6
S. Schwarzengrund	1
S. dysenteriae *	2
E. coli	1
V. cholerae *	13
V. parahaemolyticus	4

**Table S7. Number of toxin-antitoxin (TA) systems in “bad bugs” and in controls.**

\*: “bad bugs” having more TA systems compared to their controls

	Protein	CG %	GC % ref.	found in	function	Functional category
	<b>Specific non-pathogen</b>					
1	Trans-2-enoyl-CoA-reductase	62.7%	67% (M. smegmatis)	$\alpha$ -proteobacteria, Actinobacteria, nematodes, flies, primates	oxidoreductase	Energy production and onversion
2	Thioredoxin reductase	69%	67% (M. smegmatis)	Actinobacteria, $\alpha/\delta$ -proteobacteria, cyanobacteria	oxidoreductase	Posttranslational modification

A

	Protein	CG %	CG % ref.	originated species	found in	function	Functional category
1	Rhamnolipids biosynthesis – 3-oxoloacyl reductase	66.3%	67% (M. smegmatis)	fungi	$\gamma/\alpha$ -proteobacteria, Actinobacteria, Spirochetes	Rhamnolipids biosynthesis	Lipid transport and metabolism
2	Cinnamoyl-ester-hydrolase	52%	37.9% (T. denticola)	Firmicutes	Bacteroidetes, Spirochetes	hydrolase	Lipid transport and metabolism
3	Pentachlorophenol-4-monooxygenase	67.2%	67% (M. smegmatis)	Actinobacteria	$\beta/\delta$ -proteobacteria,, Firmicutes	oxidoreductase	Energy production and conversion
4	6-hydroxy-D-nicotine oxidase	68.1%	67% (M. smegmatis)	fungi	$\alpha/\beta$ -proteobacteria, Actinobacteria	oxidoreductase	Energy production and conversion
5	Methionin-S-oxide-reductase	53%	53% (T. pallidum)	$\delta$ -proteobacteria or Bacillus	$\alpha/\beta/\gamma$ -proteobacteria, Spirochetes, Actinobacteria, fungi, protists, Archaea	oxidoreductase	Posttranslational modification

B

**Table S8. Specific control species genes (A) and HGT (B).**

Bacteria	photoreactivation		Mismatch excision repair							base excision repair			nucleotide excision repair						
	PhrB	$\Sigma$	MutS	MutL	MutH	UvrD	SbcB	MutT	$\Sigma$	Ung	MutY	MutM	$\Sigma$	UvrA	UvrB	UvrC	UvrD	MFD	$\Sigma$
M. leprae	0	<b>0</b>	0	0	0	0	1	0	<b>1</b>	0	1	1	<b>2</b>	1	1	1	0	1	<b>4</b>
M. avium	1	<b>1</b>	0	0	0	1	1	1	<b>3</b>	0	1	0	<b>1</b>	1	1	1	1	0	<b>5</b>
M. tuberculosis	0	<b>0</b>	0	0	0	1	0	1	<b>2</b>	1	1	0	<b>2</b>	1	1	1	1	1	<b>5</b>
M. smegmatis	1	<b>1</b>	0	0	0	1	0	0	<b>1</b>	1	1	1	<b>3</b>	1	1	1	1	1	<b>4</b>
R. prowazekii	0	<b>0</b>	0	0	0	1	0	0	<b>1</b>	0	0	0	<b>0</b>	0	1	1	1	1	<b>4</b>
R. africae	0	<b>0</b>	0	0	0	1	0	0	<b>1</b>	0	0	0	<b>0</b>	0	1	1	1	1	<b>4</b>
C. diphtheriae	0	<b>1</b>	0	0	0	0	0	0	<b>0</b>	1	0	0	<b>1</b>	1	1	1	0	1	<b>4</b>
C. glutamicum	0	<b>1</b>	0	0	0	0	0	0	<b>0</b>	1	1	0	<b>2</b>	1	1	1	0	1	<b>3</b>
T. pallidum	0	<b>0</b>	0	0	1	0	0	1	<b>2</b>	0	0	1	<b>1</b>	1	1	1	0	0	<b>5</b>
T. denticola	0	<b>0</b>	1	0	0	1	0	1	<b>3</b>	0	0	0	<b>0</b>	1	1	1	1	1	<b>5</b>
Y. pestis	1	<b>1</b>	1	1	1	1	1	1	<b>6</b>	1	1	0	<b>2</b>	1	1	1	1	1	<b>5</b>
Y.pseudotuberculosis	1	<b>1</b>	0	0	1	1	1	1	<b>4</b>	1	0	0	<b>1</b>	1	1	1	1	1	<b>5</b>
B. pertussis	0	<b>0</b>	1	1	1	1	0	0	<b>4</b>	0	1	1	<b>2</b>	1	1	1	1	1	<b>5</b>
B. bronchiseptica	0	<b>0</b>	1	1	1	1	0	0	<b>4</b>	0	1	1	<b>2</b>	1	1	1	1	1	<b>5</b>
S. pneumoniae	0	<b>0</b>	1	1	1	1	0	0	<b>4</b>	1	1	1	<b>3</b>	1	1	1	1	1	<b>5</b>
S. agalactiae	0	<b>0</b>	1	1	1	1	0	0	<b>4</b>	0	0	0	<b>0</b>	1	1	1	1	1	<b>4</b>
S. pyogenes	1	<b>1</b>	1	1	1	0	0	0	<b>3</b>	1	1	0	<b>2</b>	1	1	1	0	1	<b>5</b>
S. suis	0	<b>0</b>	1	1	0	1	0	1	<b>4</b>	1	0	1	<b>2</b>	1	1	1	1	1	<b>5</b>
S. Typhi	1	<b>1</b>	1	1	0	1	1	1	<b>5</b>	1	1	0	<b>2</b>	1	1	1	1	1	<b>5</b>
S. Schwarzengrund	1	<b>1</b>	1	1	1	1	1	1	<b>6</b>	1	1	1	<b>3</b>	1	1	1	1	1	<b>5</b>
S. dysenteriae	1	<b>1</b>	1	1	1	1	1	1	<b>6</b>	0	1	1	<b>2</b>	1	1	1	1	1	<b>5</b>
E. coli	1	<b>1</b>	1	1	1	1	1	1	<b>6</b>	1	1	1	<b>3</b>	1	1	1	1	1	<b>5</b>
V. cholerae	1	<b>1</b>	1	1	1	1	1	1	<b>6</b>	1	1	0	<b>2</b>	1	1	1	1	1	<b>5</b>
V.parahaemolyticus	1	<b>1</b>	1	1	1	1	1	1	<b>6</b>	1	1	0	<b>2</b>	1	1	1	1	1	<b>4</b>

	Recombinational repair										$\Sigma$	Other repair				$\Sigma$
	RecB	RecC	RecD	SbcB	SbcC	SbcD	RecA	RecR	RecO	RecN		UmuC	UmuD	LexA	RadA	
M. leprae	0	0	0	1	0	0	0	1	0	0	2	0	0	1	1	2
M. avium	1	1	0	1	0	0	1	0	0	0	4	0	0	0	1	1
M. tuberculosis	1	1	1	0	0	0	1	0	0	0	4	0	0	1	1	2
M. smegmatis	0	0	1	0	0	0	1	0	0	0	2	0	1	1	1	3
R. prowazekii	0	0	0	0	0	0	1	1	1	1	4	0	0	0	1	1
R. africae	0	0	0	0	0	0	1	1	1	1	4	0	0	0	1	1
C. diphtheriae	0	0	0	0	0	1	1	0	0	0	2	0	0	1	1	2
C. glutamicum	1	0	0	0	0	0	1	1	0	0	3	0	0	1	1	2
T. pallidum	0	0	0	0	0	0	1	0	0	0	1	0	1	0	1	2
T. denticola	0	0	0	0	1	1	1	1	0	0	4	0	0	0	1	1
Y. pestis	1	1	1	1	1	1	1	1	0	0	7	1	0	1	1	3
Y.pseudotuberculosis	1	1	1	1	1	1	1	1	0	0	7	0	0	1	1	2
B. pertussis	0	0	0	0	1	0	1	1	0	0	3	0	0	1	1	2
B. bronchiseptica	0	0	0	0	1	0	1	1	0	0	3	0	0	1	1	2
S. pneumoniae	0	0	0	0	0	0	1	0	0	0	1	0	0	1	1	2
S. agalactiae	0	0	1	0	0	0	1	1	0	0	3	0	0	1	1	2
S. pyogenes	1	1	1	0	0	1	1	1	0	0	6	0	0	1	1	2
S. suis	0	0	1	0	0	0	1	1	0	0	3	1	0	0	1	2
S. Typhi	1	1	0	1	1	1	1	0	0	0	6	1	1	1	1	4
S. Schwarzengrund	1	1	1	1	1	1	1	0	0	0	7	1	1	1	1	4
S. dysenteriae	1	1	1	1	1	0	1	0	0	0	6	1	1	1	1	4
E. coli	1	1	1	1	1	1	1	0	0	0	7	1	1	1	1	4
V. cholerae	0	1	1	1	0	0	1	0	0	0	4	0	0	1	1	2
V.parahaemolyticus	1	1	1	1	0	0	1	0	0	0	5	0	0	1	1	2

**Table S9. Database of repair, replication and recombination genes.**

1: gene present, 0: gene absent,  $\Sigma$ : total number of genes

Networks	Genes	Species		Functions	Functional category
		Bad bugs	Controls		
1	KatE SodA starvation induced DNA protecting protein Soj		M. avium E. coli M. avium/ M. smegmatis M. avium	catalase HPII superoxide dismutase response to stress regulator protein	inorganic ion transport and <b>metabolism</b> cell cycle control
2	2-oxo-hepta-3-ene-1,7-dioic hydratase feruloyl-CoA synthetase		M. avium/M. smegmatis/ E. coli M. avium/M. smegmatis	aromatic compound catabolism catalytic activity	secondary metabolites transport and <b>metabolism</b>
3	Xaa-Pro dipeptidase Oxygenase KshA Rieske [2Fe-2S]domain containing protein		M. avium/M. smegmatis M. avium M. avium	dipeptidase activity oxidoreductase activity oxidoreductase activity	secondary metabolites transport and <b>metabolism</b> inorganic ion transport and <b>metabolism</b>
4	TobE protein ThiS family protein		M. avium/M. smegmatis C. glutamicum	Transport	coenzyme transport and <b>metabolism</b>
5	Threonine synthase LtaE  Tat-translocated enzyme		T. denticola S. agalactiae/ S. suis M. avium/ Y. pseudotuberculosis/ S. pneumoniae	amino acid biosynthesis L-threonine aldolase  iron iron binding	amino acid transport and <b>metabolism</b> inorganic ion transport and <b>metabolism</b>
6	Histone deacetylase argR (arginine repressor)		M. avium E. coli	transcription regulation transcription regulation	chromatine structure transcription
7	PemK family protein  CutC		T. denticola  T. denticola	DNA-binding  copper homeostasis protein	signal transduction mecanisms inorganic ion transport and <b>metabolism</b>
8	dam2 integral membrane protein chromate transport protein		R. africae T. denticola	site-specific DNA alanine methylase membrane protein transporter activity	replication, recombination general prediction inorganic ion transport and <b>metabolism</b>
9	plasmid maintenance system antidote protein 6-aminohexanoate-cyclic dimer hydrolase		R africae M. avium/M. smegmatis	DNA binding hydrolase activity	general prediction translation
10	putative virulence protein oxygen-independent coproporphyrinogen		R. africae	pathogenesis oxidoreductase	General prediction coenzyme transport and <b>metabolism</b>
11	TcpJ (type 4 prepilin leader peptide processing) TcpA (toxin coregulated pilus A)	V. cholerae V. cholerae		endopeptidase activity pathogenesis	intracellular trafficking cell motility

**Table S10. Networks containing proteins that are either found only in the controls (1-7) or only in the “bad bugs” (8) of each pair.**

		Species			
	Genes	Bad bugs	Controls	Functions	Functional category
1	VirS	M. tuberculosis		virulence regulating transcriptional regulator	Transcription
2	2-component response regulator	V. cholerae		transcription regulator	Transcription
3	plasmid replication protein	C. diphtheriae		protein polymerisation	Transcription
4	DNA-binding bacteriophage	C. diphtheriae			Transcription
5	SigI	M. tuberculosis		transcription initiation	Transcription
6	lantibiotic ABC transporter ATP-binding	C. diphtheriae		bacteriocin transport	defense mechanisms
7	DNA methyltransferase	C. diphtheriae			defense mechanisms
8	HsdS restriction modification system	C. diphtheriae		DNA methylase	defense mechanisms
9	drug transport protein	M.leprae/M.tuberculosis			defense mechanisms
10	penicillin binding protein	M. tuberculosis		penicillin binding	defense mechanisms
11	lipoprotein	M. tuberculosis		pathogenesis	defense mechanisms
12	FliS protein	Y. pestis		flagellum assembly	intracellular trafficking
13	peptidase	S. Typhi			cell cycle control
14	protein methionine-S-oxide reductase	T. pallidum		oxidation reduction	Posttranslational modifications
15	tail fiber assembly protein	S.dysenteriae/V.cholerae			RNA processing and modification
16	vibriobactin and enterobactin ABC transporter	V. cholerae		high affinity iron ion transport	inorganic ion transport and metabolism
17	phosphoribosylpyrophosphate synthase	V. cholerae			amino acid transport and metabolism
18	nickel hydrogenase incorporation		M. avium/M. smegmatis/C. glutamicum	cofactor biosynthetic process	Transcription
19	ATP-dependent helicase DING		E. coli	DNA recombination	Transcription
20	SigJ		M. avium	transcription initiation	Transcription
21	diphtheria toxin repressor		M. avium	regulation of transcription	Transcription

<b>22</b>	DNA-directed RNA pol. Su beta'		<i>E. coli</i>	regulation of transcription	Transcription
<b>23</b>	transcriptional regulator		<i>R. africae</i>	regulation of transcription	Transcription
<b>24</b>	SpoT15		<i>R. africae</i>	Guanosine polyphosphate pyrophosphate hydrolase	Transcription
<b>25</b>	Ankyrin repeat		<i>R. africae</i>	protein-protein interaction	General prediction
<b>26</b>	flagellar assembly protein H (FliH)		<i>V. parahaemolyticum</i>	flagellar motility	intracellular trafficking
<b>27</b>	inner membrane protein		<i>T. denticola</i>		intracellular trafficking
<b>28</b>	outer membrane usher protein precursor		<i>E. coli</i>		intracellular trafficking
<b>29</b>	chaperone protein		<i>E. coli</i>	response to stress	intracellular trafficking
<b>30</b>	hemolysin activator like		<i>E. coli/V. parahaemolyticum</i>		intracellular trafficking
<b>31</b>	type IV prepilin peptidase		<i>V. parahaemolyticum</i>		intracellular trafficking
<b>32</b>	transmembrane protein		<i>M. avium</i>		cell cycle control
<b>33</b>	nucleotide binding protein		<i>T. denticola</i>		cell cycle control
<b>34</b>	cell division initiation		<i>S. suis</i>		cell cycle control
<b>35</b>	MukB		<i>S. schwarzengrund</i>	chromosome partition protein	cell cycle control
<b>36</b>	septum site determining		<i>E. coli</i>		cell cycle control
<b>37</b>	UDP-N-acetylglycosamine acyltransferase		<i>E. coli</i>		cell wall biogenesis
<b>38</b>	ABC transporter ATP-binding		<i>S. suis/B. bronchiseptica</i>		cell wall biogenesis
<b>39</b>	large conductance mechanosensitive channel		<i>M. avium</i>	Ion transport	cell wall biogenesis
<b>40</b>	capsular polysaccharide biosynthesis glycos		<i>E. coli</i>	polysaccharide biosynthetic protein	cell wall biogenesis
<b>41</b>	major facilitator superfamily protein		<i>M. smegmatis</i>		signal transduction
<b>42</b>	PspC domain containing protein		<i>T. denticola</i>		signal transduction
<b>43</b>	P22 repressor		<i>Y.</i>		signal transduction



			pseudotuberculosis		
44	HTH-DNA binding domain containing		<i>E. coli</i>	transcriptional regulator	signal transduction
45	mannitol-2-dehydrogenase		<i>M. avium</i>	oxidoreductase	carbohydrate transport and metabolism
46	HAMP domain/ EAL domain protein		<i>T. denticola</i>	signal transducer activity	cell motility
47	pentachlorophenol-4-monooxygenase		<i>M. smegmatis</i>	oxidation reduction	energy production and conversion
48	6-hydroxy-D-nicotine oxidase		<i>M. smegmatis</i>	oxidation reduction	energy production and conversion
49	trans-2-enoyl-CoA-reductase		<i>M. smegmatis</i>	oxidoreductase	energy production and conversion
50	Dihydropyrimidinase		<i>M. smegmatis</i>	dihydropyrimidinase activity	nucleotide transport and metabolism
51	thioredoxin reductase		<i>M. smegmatis</i>	oxidoreductase	Posttranslational modifications
52	cinnamoyl-ester hydrolase		<i>T. denticola</i>	hydrolase activity	lipid metabolism and transport
53	para-nitrobenzylesterase		<i>M. avium</i>		lipid metabolism and transport
54	rhamnolipids biosynthesis 3-oxaloacyl reduct		<i>M. avium</i>		lipid metabolism and transport
55	phage related membrane protein		<i>B. bronchispetica</i>		Chromatine structure
56	phage related DNA-binding		<i>B. bronchispetica</i>		Chromatine structure
57	autotransporter adhesin		<i>E. coli</i>		extracellular structure
58	Hemagglutin		<i>E. coli</i>		extracellular structure
59	von Willebrand factor type A domain containin		<i>M. avium/M. smegmatis</i>		inorganic ion transport and metabolism
60	superoxide dismutase		<i>E. coli</i>	oxidation reduction	inorganic ion transport and metabolism
61	NADH dehydrogenase subunit L		<i>M. avium</i>		inorganic ion transport and metabolism

<b>62</b>	lipolytic enzyme		M. avium/M. smegmatis/ C. glutamicum/ B.bronchiseptica		inorganic ion transport and metabolism
<b>63</b>	Cyclododecanone monooxygenase		M. avium/M. smegmatis	oxidation reduction	inorganic ion transport and metabolism
<b>64</b>	KtrA		V. parahaemolyticum	pottasium uptake protein	inorganic ion transport and metabolism
<b>65</b>	TrkH		T. denticola	Trk system potassium uptake protein	inorganic ion transport and metabolism
<b>66</b>	Ferritin		T. denticola		inorganic ion transport and metabolism
<b>67</b>	hemerythrin-related		T. denticola	metal ion binding	inorganic ion transport and metabolism
<b>68</b>	FeoA		T. denticola	iron ion binding	inorganic ion transport and metabolism
<b>69</b>	rhodanese like domain containing protein		T. denticola		inorganic ion transport and metabolism
<b>70</b>	peptide ABC transporter		T. denticola		inorganic ion transport and metabolism
<b>71</b>	4-hydroxyphenylacetate degradation		E. coli	decarboxylase	Ilary metabolites transport and metabolism
<b>72</b>	TauD/TfdA		M. avium	taurine catabolism dioxygenase	Ilary metabolites transport and metabolism
<b>73</b>	carveol dehydrogenase		M. avium/ B. bronchiseptica	dehydrogenase activity	Ilary metabolites transport and metabolism
<b>74</b>	carotenoid oxygenase		M. avium	oxygenase activity	Ilary metabolites transport and metabolism
<b>75</b>	arylamine N-acetyltransferase		M. avium/E. coli	acetyltransferase activity	Ilary metabolites transport and metabolism
<b>76</b>	3-alpha-hydroxysteroid dehydrogenase		M. avium/ M. smegmatis	oxidation reduction	Ilary metabolites transport and metabolism
<b>77</b>	2,5-dichloro-2,5-cyclohexadiene-1,4-diol dH		M. avium/ M. smegmatis	oxidation reduction	Ilary metabolites transport and metabolism

<b>78</b>	P450 heme thiolate protein		M.avium		Many metabolites transport and metabolism
<b>79</b>	retinal pigment epithelium membrane protein		M. avium/ M. smegmatis		Many metabolites transport and metabolism
<b>80</b>	linear gramicidin synthetase subunit B		M. avium/ M. smegmatis	isomerase, ligase activity	Many metabolites transport and metabolism
<b>81</b>	queuine Trna-ribosyltransferase		M. avium/ M. smegmatis	biosynthetic protein	Translation
<b>82</b>	selenocysteine-specific translation		M. avium/ M. smegmatis	elongation factor	Translation
<b>83</b>	GCN5-related-N-acetyltransferase		M. avium/ M. smegmatis	metabolic process	Translation
<b>84</b>	thiopurine S-methyltransferase		M. avium	metabolic process	coenzyme transport and metabolism
<b>85</b>	D-isomer specific 2-hydroxyacid dH family		M. avium/ M. smegmatis	oxidoreductase	coenzyme transport and metabolism
<b>86</b>	precorrin 6A-synthetase		M. avium/ M. smegmatis		coenzyme transport and metabolism
<b>87</b>	glycoylase family		M. avium/ M. smegmatis		amino acid transport and metabolism
<b>88</b>	selenide, water dikinase		M. avium/ M. smegmatis		amino acid transport and metabolism
<b>89</b>	gamma-glutamyltransferase		M. avium		amino acid transport and metabolism
<b>90</b>	3-isopropylmalate dehydrogenase small su		M. avium/ M. smegmatis	oxidation reduction	amino acid transport and metabolism
<b>91</b>	Orn/Lys/Arg decarboxylase		M. avium/ M. smegmatis	decarboxylase	amino acid transport and metabolism
<b>92</b>	B12-dependent methionine synthetase		M. avium/ M. smegmatis		amino acid transport and metabolism
<b>93</b>	dihydrodipicolinate synthase family protein		M. avium/ M. smegmatis	synthase activity	amino acid transport and metabolism
<b>94</b>	cystathionine gamma-lyase		M. avium	lyase activity	amino acid transport and metabolism

<b>95</b>	choline dehydrogenase		<i>M. avium/ M. smegmatis</i>	oxidation reduction	amino acid transport and metabolism
<b>96</b>	chorismate synthase		<i>T. denticola</i>	synthase activity	amino acid transport and metabolism
<b>97</b>	3-phosphoshikinate 1-carboxyvinyltransferase		<i>T. denticola</i>		amino acid transport and metabolism
<b>98</b>	shikimate kinase		<i>T. denticola</i>	biosynthetic process	amino acid transport and metabolism
<b>99</b>	ornithine cyclodeaminase		<i>T. denticola</i>	cyclodeaminase activity	amino acid transport and metabolism
<b>100</b>	L-threonine O-3-phosphate decarboxylate		<i>T. denticola</i>	decarboxylase	amino acid transport and metabolism
<b>101</b>	aromatic amino acid aminotransferase		<i>S. suis</i>	transferase activity	amino acid transport and metabolism
<b>102</b>	Cell surface antigen Sca2		<i>R. africae</i>	autotransportase domain	Unknown

**Table S11. Genes found only in “bad bugs” or only in the control species.**

<b>COGs</b>	<b>COG description</b>	<b>Found in</b>
COG2264	Ribosomal protein L11 methylase (J)	<i>Y. pestis</i> , <i>Y. pseudotuberculosis</i> , <i>B. bronchiseptica</i>
COG1188	Ribosome-associated heat shock protein implicated in the recycling of the 50S subunit (S4 paralog) (J)	<i>B. bronchiseptica</i> , <i>B. pertussis</i> , <i>Y. pestis</i> , <i>Y. pseudotuberculosis</i> ; <i>V. parahaemolyticus</i> , <i>V. cholerae</i> , <i>C. glutamicum</i> , <i>C. Diphtheriae</i> , <i>E. coli</i> , <i>S. Typhi</i>
COG2265 #	SAM-dependent methyltransferases related to tRNA (uracil-5-)-methyltransferase (J)	<i>M. smegmatis</i> , <i>M. avium</i> , <i>M. tuberculosis</i> , <i>C. glutamicum</i> , <i>C. diphtheriae</i> , <i>T. denticola</i> , <i>V. parahaemolyticus</i> , <i>V. cholerae</i> , <i>S. pneumoniae</i> , <i>S. pyogenes</i> , <i>S. agalactiae</i> , <i>S. suis</i> , <i>E. coli</i> , <i>S. dysenteriae</i> , <i>B. pertussis</i> , <i>S. Typhi</i> , <i>S. Schwarzengrund</i>
COG1595 *	DNA-directed RNA polymerase specialized sigma subunit, sigma24 homolog (K)	<i>B. bronchiseptica</i> , <i>B. pertussis</i> , <i>C. glutamicum</i> , <i>M. leprae</i>
COG1508 #	DNA-directed RNA polymerase specialized sigma subunit, sigma54 homolog (K)	<i>Y. pestis</i> , <i>Y. pseudotuberculosis</i> , <i>V. parahaemolyticus</i> , <i>V. cholerae</i> , <i>B. bronchiseptica</i> , <i>B. pertussis</i> , <i>E. coli</i> , <i>S. dysenteriae</i> , <i>T. pallidum</i> , <i>T. Denticola</i> , <i>S. Typhi</i> , <i>S. Schwarzengrund</i>
COG1522	Transcriptional regulators (K)	<i>V. parahaemolyticus</i> , <i>V. cholerae</i> , <i>B. bronchiseptica</i> , <i>B. pertussis</i> , <i>E. coli</i> , <i>Y. pestis</i> , <i>Y. pseudotuberculosis</i> , <i>M. tuberculosis</i> , <i>S. Typhi</i> , <i>S. Schwarzengrund</i>
COG1167	Transcriptional regulators containing a DNA-binding HTH domain and an aminotransferase domain (MocR family) and their eukaryotic orthologs (KE)	
COG1974 *	SOS-response transcriptional repressors (RecA-mediated autopeptidases) (KT)	<i>S. pneumoniae</i> , <i>M. smegmatis</i> , <i>M. tuberculosis</i> , <i>M. avium</i> , <i>M. leprae</i> , <i>C. diphtheriae</i> , <i>B. bronchiseptica</i> , <i>B. pertussis</i> , <i>S. Typhi</i> , <i>S. Schwarzengrund</i>
COG1643	HrpA-like helicases (L)	<i>Y. pseudotuberculosis</i> , <i>Y. pestis</i> , <i>E. coli</i> , <i>S. dysenteriae</i> , <i>B. bronchiseptica</i> , <i>B. pertussis</i> , <i>V. parahaemolyticus</i> , <i>V. cholerae</i> , <i>M. avium</i> , <i>M. smegmatis</i> , <i>C. glutamicum</i> , <i>C. diphtheriae</i> , <i>S. Typhi</i> , <i>S. Schwarzengrund</i>
COG0277 * #	FAD/FMN-containing dehydrogenases (C)	<i>M. smegmatis</i> , <i>M. leprae</i> , <i>M. avium</i> , <i>M. tuberculosis</i> , <i>T. denticola</i> , <i>E. coli</i> , <i>B. bronchiseptica</i> , <i>B. pertussis</i>
COG0247 *	Fe-S oxidoreductase (C)	<i>M. smegmatis</i> , <i>M. leprae</i> , <i>E. coli</i> , <i>C. diphtheriae</i> , <i>S. Typhi</i> , <i>S. Schwarzengrund</i>
COG2225 *	Malate synthase (C)	<i>V. cholerae</i> , <i>V. parahaemolyticus</i> , <i>E. coli</i> , <i>Y. pseudotuberculosis</i> , <i>Y. pestis</i> , <i>S. dysenteriae</i> , <i>M. leprae</i> , <i>S. Typhi</i> , <i>S. Schwarzengrund</i>
COG1902	NADH:flavin oxidoreductases, Old Yellow Enzyme family (C)	<i>B. bronchiseptica</i> , <i>Y. pseudotuberculosis</i> , <i>Y. pestis</i> , <i>C. glutamicum</i> , <i>E. coli</i> , <i>S. Typhi</i> , <i>S.</i>

		Schwarzengrund
COG0778 *	Nitroreductase (C)	S. dysenteriae, E. coli, M. leprae, S. Typhi, S. Schwarzengrund
COG2352 *	Phosphoenolpyruvate carboxylase (C)	M. leprae, M. smegmatis, M. avium, S. suis, S. pneumoniae, S. agalactiae, C. diphtheriae, C. glutamicum, B. pertussis, B. bronchiseptica, S. pyogenes, V. parahaemolyticus, V. cholerae, S. dysenteriae, Y. pseudotuberculosis, S. Typhi, S. Schwarzengrund
COG1600	Uncharacterized Fe-S protein (C)	E. coli, S. dysenteriae, Y. pestis, Y. pseudotuberculosis, V. cholerae, V. parahaemolyticus, S. pyogenes, S. agalactiae, S. suis
COG1062 *	Zn-dependent alcohol dehydrogenases, class III (C)	M. leprae, M. avium, M. tuberculosis, M. smegmatis, B. bronchiseptica, B. pertussis, Y. pseudotuberculosis, Y. pestis, C. Glutamicum, E. coli, S. suis, S. pneumoniae, S. pyogenes, S. Schwarzengrund
COG0239	Integral membrane protein possibly involved in chromosome condensation (D)	
COG0683	ABC-type branched-chain amino acid transport systems, periplasmic component (E)	S. suis, S. pneumoniae, M. smegmatis, S. agalactiae, S. dysenteriae
COG1176	ABC-type spermidine/putrescine transport system, permease component I (E)	V. cholerae, V. parahaemolyticus, E. coli, S. dysenteriae, Y. pestis, Y. pseudotuberculosis, S. pneumoniae, S. pyogenes, S. suis, S. agalactiae, S. Typhi, S. Schwarzengrund
COG1177	ABC-type spermidine/putrescine transport system, permease component II (E)	V. parahaemolyticus, Y. pestis, Y. pseudotuberculosis, T. pallidum, E. coli, S. dysenteriae, B. bronchiseptica, V. cholerae, C. glutamicum, M. smegmatis, S. Typhi, S. Schwarzengrund
COG2049 *	Allophanate hydrolase subunit 1 (E)	B. pertussis, B. bronchiseptica, M. tuberculosis, M. avium, M. smegmatis, M. leprae, E. coli, S. dysenteriae, Y. pseudotuberculosis, Y. pestis, C. glutamicum, V. cholerae, S. Typhi, S. Schwarzengrund
COG1984 *	Allophanate hydrolase subunit 2 (E)	Y. pseudotuberculosis, Y. pestis, E. coli, S. dysenteriae, V. cholerae, V. parahaemolyticus, B. bronchiseptica, B. pertussis, M. tuberculosis, M. avium, M. leprae, S. Typhi, S. Schwarzengrund
COG2303	Choline dehydrogenase and related flavoproteins (E)	
COG0014 *	Gamma-glutamyl phosphate reductase (E)	E. coli, S. agalactiae, Y. pseudotuberculosis, Y. pestis, S. pyogenes, V. cholerae, V. parahaemolyticus, S. pneumoniae, S. suis, B. pertussis, B. bronchiseptica, T. pallidum, M. leprae, S. Typhi, S.

		Schwarzengrund
COG0405	Gamma-glutamyltransferase (E)	E. coli, S. dysenteriae, Y. pseudotuberculosis, Y. pestis, V. parahaemolyticus, V. cholerae, B. pertussis, B. bronchiseptica, M. tuberculosis, M. avium, M. smegmatis, C. glutamicum
COG0263 *	Glutamate 5-kinase (E)	M. leprae, M. smegmatis, M. avium, M. tuberculosis, V. cholerae, E. coli, B. bronchiseptica, B. pertussis, Y. pestis, S. pneumoniae, S. suis, S. agalactiae, S. pyogenes, C. glutamicum
COG0665	Glycine/D-amino acid oxidases (deaminating) (E)	B. bronchiseptica, B. pertussis, V. parahaemolyticus, S. dysenteriae, E. coli, S. Typhi, S. Schwarzengrund
COG0346 *	Lactoylglutathione lyase and related lyases (E)	M. leprae, M. avium, S. Schwarzengrund
COG2755 *	Lysophospholipase L1 and related esterases (E)	M. leprae
COG1410 *	Methionine synthase I, cobalamin-binding domain (E)	M. leprae, M. smegmatis, M. avium, M. tuberculosis, B. bronchiseptica, B. pertussis, V. cholerae, V. parahaemolyticus, E. coli, Y. pestis, Y. pseudotuberculosis, S. Typhi, S. Schwarzengrund
COG0347	Nitrogen regulatory protein PII (E)	V. cholerae, E. coli, S. dysenteriae, B. pertussis, B. bronchiseptica, V. parahaemolyticus, Y. pseudotuberculosis, Y. pestis, C. glutamicum, C. diphtheriae, M. tuberculosis, M. smegmatis, S. Typhi, S. Schwarzengrund
COG1280	Putative threonine efflux protein (E)	V. cholerae, Y. pestis, Y. pseudotuberculosis
COG2008 #	Threonine aldolase (E)	M. smegmatis, T. denticola, S. agalactiae, S. suis
COG1762 #	Phosphotransferase system mannitol/fructose-specific IIA domain (Ntr-type) (GT)	T. denticola, V. parahaemolyticus
COG0315	Molybdenum cofactor biosynthesis enzyme (H)	V. cholerae, M. avium, M. tuberculosis, Y. pseudotuberculosis, Y. pestis, E. coli, C. glutamicum, M. smegmatis, C. diphtheriae, S. Typhi, S. Schwarzengrund
COG2896	Molybdenum cofactor biosynthesis enzyme (H)	M. tuberculosis, M. avium, M. smegmatis, C. diphtheriae, C. glutamicum, B. bronchiseptica, B. pertussis, E. coli, S. dysenteriae, V. cholerae, V. parahaemolyticus, Y. pestis, Y. pseudotuberculosis, S. Typhi
COG0303*	Molybdopterin biosynthesis enzyme (H)	M. leprae, M. avium, M. tuberculosis, E. coli, Y. pseudotuberculosis, Y. pestis, B. bronchiseptica, B. pertussis, V. cholerae, C. diphtheriae, C. glutamicum, S. Typhi, S. Schwarzengrund

COG0521 *	Molybdopterin biosynthesis enzymes (H)	M. leprae, M. avium, M. tuberculosis, M. smegmatis, V. cholerae, V. parahaemolyticus, E. coli, S. dysenteriae, B. bronchiseptica, B. pertussis, Y. pestis, Y. pseudotuberculosis, C. glutamicum
COG0314	Molybdopterin converting factor, large subunit (H)	V. cholerae, V. parahaemolyticus, E. coli, S. dysenteriae, Y. pestis, Y. pseudotuberculosis, B. bronchiseptica, B. Pertussis
COG1977	Molybdopterin converting factor, small subunit (H)	
COG0746	Molybdopterin-guanine dinucleotide biosynthesis protein A (H)	
COG2267 *	Lysophospholipase (I)	M. leprae, M. tuberculosis, M. smegmatis, M. avium, C. diphtheriae, S. Typhi, S. Schwarzengrund
COG0318	Acyl-CoA synthetases (AMP-forming)/AMP-acid ligases II (IQ)	S. Typhi, S. Schwarzengrund
COG2230 *	Cyclopropane fatty acid synthase and related methyltransferases (M)	V. parahaemolyticus, Y. pestis, V. cholerae, Y. pseudotuberculosis, E. coli, S. dysenteriae, S. agalactiae, C. glutamicum, B. bronchiseptica, B. pertussis, M. avium, M. tuberculosis, M. leprae, S. Typhi, S. Schwarzengrund
COG1596	Periplasmic protein involved in polysaccharide export (M)	
COG0810	Periplasmic protein TonB, links inner and outer membranes (M)	S. Typhi, S. Schwarzengrund
COG1247	Sortase and related acyltransferases (M)	E. coli, S. dysenteriae, C. glutamicum, C. diphtheriae, B. bronchiseptica, B. pertussis, V. cholerae, S. Typhi, S. Schwarzengrund
COG2148	Sugar transferases involved in lipopolysaccharide synthesis (M)	V. cholerae, S. pneumoniae, S. suis, S. agalactiae, V. parahaemolyticus, C. glutamicum, S. Typhi, S. Schwarzengrund
COG3206	Uncharacterized protein involved in exopolysaccharide biosynthesis (M)	E. coli, S. dysenteriae, C. glutamicum, V. parahaemolyticus, V. cholerae, S. agalactiae, S. pneumoniae
COG1580	Flagellar basal body-associated protein (N)	B. bronchiseptica, B. pertussis, S. Typhi, S. Schwarzengrund
COG1291	Flagellar motor component (N)	B. bronchiseptica, E. coli, Y. pseudotuberculosis, Y. pestis, S. dysenteriae, V. parahaemolyticus
COG1344	Flagellin and related hook-associated proteins (N)	
COG0643 #	Chemotaxis protein histidine kinase and related kinases (NT)	V. cholerae, Y. pestis, Y. pseudotuberculosis, E. coli, T. denticola, T. Pallidum, S. Typhi, S. Schwarzengrund
COG2201	Chemotaxis response regulator containing a CheY-like receiver domain and a methylesterase domain (NT)	T. pallidum, V. parahaemolyticus, V. cholerae
COG0835 #	Chemotaxis signal transduction	V. parahaemolyticus, V. cholerae,



	protein (NT)	E. coli, Y. pestis, Y. pseudotuberculosis, B. bronchiseptica, T. pallidum, T. denticola, S. Typhi, S. Schwarzengrund
COG0840 #	Methyl-accepting chemotaxis protein (NT)	V. cholerae, V. parahaemolyticus, E. coli, T. denticola, S. dysenteriae
COG1352 #	Methylase of chemotaxis methyl-accepting proteins (NT)	V. cholerae, E. coli, Y. pestis, Y. pseudotuberculosis, B. pertussis, T. denticola, T. pallidum, V. parahaemolyticus, M. smegmatis, M. avium, S. Typhi, S. Schwarzengrund
COG0229	Conserved domain frequently associated with peptide methionine sulfoxide reductase (O)	E. coli, S. dysenteriae, V. parahaemolyticus, V. cholerae, Y. pestis, Y. pseudotuberculosis, S. suis, S. pyogenes, S. pneumoniae, S. Typhi, S. Schwarzengrund
COG4235	Cytochrome c biogenesis factor (O)	E. coli, S. dysenteriae, Y. pseudotuberculosis, Y. pestis, V. cholerae, V. parahaemolyticus
COG1281	Disulfide bond chaperones of the HSP33 family (O)	Y. pestis, Y. pseudotuberculosis, E. coli, S. dysenteriae, V. cholerae, V. parahaemolyticus, B. pertussis, B. bronchiseptica
COG0386 #	Glutathione peroxidase (O)	M. avium, M. smegmatis, E. coli, S. dysenteriae, C. glutamicum, C. diphtheriae, Y. pestis, Y. pseudotuberculosis, S. pyogenes, S. suis, S. pneumoniae, B. pertussis, B. bronchiseptica, T. denticola, S. Typhi, S. Schwarzengrund
COG2360 #	Leu/Phe-tRNA-protein transferase (O)	E. coli, S. dysenteriae, B. pertussis, T. denticola, Y. pestis, Y. pseudotuberculosis, V. cholerae, S. Typhi, S. Schwarzengrund
COG0652 *	Peptidyl-prolyl cis-trans isomerase (rotamase) – cyclophilin family (O)	M. leprae, E. coli, S. dysenteriae, V. parahaemolyticus, V. cholerae, B. pertussis, B. bronchiseptica, Y. pestis, Y. pseudotuberculosis, S. suis, S. pneumoniae, S. Typhi, S. Schwarzengrund
COG1764	Predicted redox protein, regulator of disulfide bond formation (O)	C. glutamicum, M. smegmatis, V. cholerae, V. parahaemolyticus
COG2518	Protein-L-isoaspartate carboxylmethyltransferase (O)	V. parahaemolyticus, Y. pestis, Y. pseudotuberculosis, V. cholerae, E. coli, S. dysenteriae, B. bronchiseptica, B. pertussis, S. Typhi
COG3118 *	Thioredoxin domain-containing protein (O)	E. coli, S. dysenteriae, Y. pestis, Y. pseudotuberculosis, V. cholerae, V. parahaemolyticus, C. glutamicum, C. diphtheriae, B. bronchiseptica, M. leprae, M. avium, M. tuberculosis, S. pyogenes, S. agalactiae, S. Typhi, S. Schwarzengrund
COG2844	UTP:GlnB (protein PII) uridylyltransferase (O)	V. cholerae, V. parahaemolyticus, E. coli, S. dysenteriae, Y. pseudotuberculosis, Y. pestis, B. bronchiseptica, B. pertussis, M.

		smegmatis, M. avium, M. tuberculosis, C. diphtheriae, C. glutamicum, S. Typhi, S. Schwarzengrund
COG1391 *	Glutamine synthetase adenylyltransferase (OT)	M. leprae, M. tuberculosis, M. smegmatis, M. avium, E. coli, V. cholerae, V. parahaemolyticus, S. dysenteriae, Y. pseudotuberculosis, Y. pestis, C. diphtheriae, B. pertussis, S. Typhi, S. Schwarzengrund
COG0725	ABC-type molybdate transport system, periplasmic component (P)	V. parahaemolyticus, V. cholerae, E. coli, Y. pestis, Y. pseudotuberculosis, S. dysenteriae, C. glutamicum, C. diphtheriae, M. avium, M. tuberculosis, M. smegmatis, S. Typhi, S. Schwarzengrund
COG0600	ABC-type nitrate/sulfonate/bicarbonate transport system, permease component (P)	B. bronchiseptica, B. pertussis, C. glutamicum, V. parahaemolyticus, Y. pestis, Y. pseudotuberculosis, M. avium, S. suis, S. pneumoniae
COG0004	Ammonia permease (P)	V. parahaemolyticus, V. cholerae, M. avium, M. smegmatis, M. tuberculosis, B. bronchiseptica, B. pertussis, C. glutamicum, E. coli, S. dysenteriae, Y. pestis, Y. pseudotuberculosis, S. Typhi, S. Schwarzengrund
COG1393 *	Arsenate reductase and related proteins, glutaredoxin family (P)	E. coli, S. dysenteriae, Y. pestis, Y. pseudotuberculosis, V. cholerae, V. parahaemolyticus, M. avium, M. smegmatis, M. leprae, B. pertussis, B. bronchiseptica, S. agalactiae, S. pyogenes, C. glutamicum, S. Typhi, S. Schwarzengrund
COG0704	Phosphate uptake regulator (P)	
COG0855 *	Polyphosphate kinase (P)	M. leprae, M. smegmatis, M. tuberculosis, M. avium, B. pertussis, B. bronchiseptica, V. parahaemolyticus, Y. pestis, Y. pseudotuberculosis, S. dysenteriae, E. coli, S. Typhi, S. Schwarzengrund
COG2897 *	Rhodanese-related sulfurtransferase (P)	M. leprae, M. avium, M. tuberculosis, B. pertussis, B. bronchiseptica, C. diphtheriae, C. glutamicum, S. dysenteriae, E. coli, V. parahaemolyticus, V. cholerae, Y. pestis, S. Typhi, S. Schwarzengrund
COG0659 *	Sulfate permease and related transporters (MFS superfamily) (P)	M. tuberculosis, M. leprae, M. avium, M. smegmatis, Y. pestis, Y. pseudotuberculosis, C. diphtheriae, C. glutamicum, S. Typhi, S. Schwarzengrund
COG0179 *	2-keto-4-pentenoate hydratase/2-oxohepta-3-ene-1,7-dioic acid hydratase (catechol pathway) (Q)	M. leprae, M. tuberculosis, S. smegmatis, E. coli, S. dysenteriae, Y. pseudotuberculosis, Y. pestis, B. bronchiseptica, B. pertussis, C. glutamicum, V. parahaemolyticus, V. cholerae, S. Typhi, S. Schwarzengrund

COG3127	Predicted ABC-type transport system involved in lysophospholipase L1 biosynthesis, permease component (Q)	E. coli, S. dysenteriae, Y. pestis, Y. pseudotuberculosis, V. parahaemolyticus, V. cholerae, B. pertussis, B. bronchiseptica, S. Typhi, S. Schwarzengrund
COG0664 *	cAMP-binding proteins – catabolite gene activator and regulatory subunit of cAMP-dependent protein kinases (T)	M. leprae, M. smegmatis, M. avium, M. tuberculosis, C. glutamicum, C. diphtheriae, Y. pestis, Y. pseudotuberculosis, E. coli, S. dysenteriae, V. cholerae, V. parahaemolyticus, S. Typhi, S. Schwarzengrund
COG5001 *	Predicted signal transduction protein containing a membrane domain, an EAL and a GGDEF domain (T)	M. leprae, M. avium, M. smegmatis, V. cholerae, V. parahaemolyticus, Y. pestis, Y. pseudotuberculosis, B. bronchiseptica, B. pertussis, E. coli, C. glutamicum, S. Typhi, S. Schwarzengrund
COG0394	Protein-tyrosine-phosphatase (T)	V. cholerae, V. parahaemolyticus, B. bronchiseptica, B. pertussis, S. agalactiae, S. pyogenes, S. pneumoniae, S. suis
COG3852 #	Signal transduction histidine kinase, nitrogen specific (T)	B. bronchiseptica, B. pertussis, Y. pestis, Y. pseudotuberculosis, E. coli, S. dysenteriae, V. cholerae, V. parahaemolyticus, M. avium, M. tuberculosis, T. denticola, T. pallidum, S. suis, S. Typhi, S. Schwarzengrund
COG1253	Hemolysins and related proteins containing CBS domains (R)	E. coli, S. dysenteriae, Y. pestis, Y. pseudotuberculosis, V. cholerae, V. parahaemolyticus, S. pyogenes, S. suis, S. agalactiae, S. pneumoniae, S. Typhi, S. Schwarzengrund
COG0714 *	MoxR-like ATPases (R)	M. leprae
COG1741	Pirin-related protein (R)	V. cholerae, V. parahaemolyticus, Y. pseudotuberculosis, Y. pestis, M. smegmatis, M. avium, B. bronchiseptica, B. pertussis, S. dysenteriae, E. coli, S. Typhi, S. Schwarzengrund
COG0388 *	Predicted amidohydrolase (R)	M. leprae, M. smegmatis, V. parahaemolyticus, V. cholerae, B. pertussis, B. bronchiseptica, Y. pseudotuberculosis, Y. pestis, S. Typhi, S. Schwarzengrund
COG2081	Predicted flavoproteins (R)	E. coli, Y. pestis, V. parahaemolyticus, V. cholerae, B. bronchiseptica, B. pertussis, S. pyogenes, S. pneumoniae, S. agalactiae, S. suis, S. Typhi, S. Schwarzengrund
COG1694	Predicted pyrophosphatase (R)	S. agalactiae
COG1611 *	Predicted Rossmann fold nucleotide-binding protein (R)	M. leprae, E. coli, S. dysenteriae, Y. pseudotuberculosis, Y. pestis, V. Cholerae, S. Typhi, S. Schwarzengrund
COG0523	Putative GTPases (G3E family) (R)	E. coli, S. dysenteriae, Y. pseudotuberculosis, Y. pestis, V. cholerae, M. smegmatis, B. bronchiseptica, B. pertussis, S.

		Typhi, S. Schwarzengrund
COG2334	Putative homoserine kinase type II (protein kinase fold) (R)	
COG1540 *	Uncharacterized proteins, homologs of lactam utilization protein B (R)	M. leprae, M. avium, M. smegmatis, C. glutamicum, B. pertussis, B. bronchiseptica, Y. pestis, E. coli, S. dysenteriae, V. parahaemolyticus, V. cholerae, S. Typhi, S. Schwarzengrund
COG0397	Uncharacterized conserved protein (S)	M. aviu., M. smegmatis, C. glutamicum, Y. pseudotuberculosis, Y. pestis, V. cholerae, E. coli, S. dysenteriae
COG1576	Uncharacterized conserved protein (S)	
COG2127 *	Uncharacterized conserved protein (S)	M. leprae, M. smegmatis, M. avium, M. tuberculosis, C. diphtheriae, C. glutamicum, S. Typhi, S. Schwarzengrund
COG2606 * #	Uncharacterized conserved protein (S)	M. leprae, T. denticola, S. Typhi, S. Schwarzengrund
COG2983	Uncharacterized conserved protein (S)	Y. pestis, Y. pseudotuberculosis, E. coli, S. dysenteriae, B. bronchiseptica, B. pertussis, V. cholerae, V. parahaemolyticus, M. avium, M. smegmatis, M. tuberculosis, C. glutamicum, C. diphtheriae, S. Typhi, S. Schwarzengrund
COG1671	Uncharacterized protein conserved in bacteria (S)	Y. pestis, Y. pseudotuberculosis, S. dysenteriae, V. parahaemolyticus, V. cholerae, T. denticola, T. pallidum, S. Typhi, S. Schwarzengrund
COG 3024	Uncharacterized protein conserved in bacteria (S)	E. coli, S. dysenteriae, Y. pestis, S. Typhi, S. Schwarzengrund

**Table S12. Set of 100 COGs that are lost in obligate intracellular bacteria.**

#: genes found in *T. denticola*, \*: genes found in *M. leprae*

<b>Genes</b>	<b>Function</b>
COG1167	Transcriptional regulators containing a DNA-binding HTH domain and an aminotransferase domain (MocR family) and their eukaryotic orthologs (KE)
COG0239	Integral membrane protein possibly involved in chromosome condensation (D)
COG2303	Choline dehydrogenase and related flavoproteins (E)
COG1977	Molybdopterin converting factor, small subunit (H)
COG0746	Molybdopterin-guanine dinucleotide biosynthesis protein A (H)
COG1596	Periplasmic protein involved in polysaccharide export (M)
COG1344	Flagellin and related hook-associated proteins (N)
COG0704	Phosphate uptake regulator (P)
COG2334	Putative homoserine kinase type II (protein kinase fold) (R)
COG1576	Uncharacterized conserved protein (S)

**Table S13. Among the set of 100 genes, ten genes were not detected in any of our 24 species.**