

References

- Achtman, M. (2008). Evolution, population structure, and phylogeography of genetically monomorphic bacterial pathogens. *Annu Rev Microbiol* 62, 53-70.
- Achtman, M., Morelli, G., Zhu, P., Wirth, T., Diehl, I., Kusecek, B., Vogler, A.J., Wagner, D.M., Allender, C.J., Easterday, W.R., *et al.* (2004). Microevolution and history of the plague bacillus, *Yersinia pestis*. *Proc Natl Acad Sci U S A* 101, 17837-17842.
- Achtman, M., and Wagner, M. (2008). Microbial diversity and the genetic nature of microbial species. *Nat Rev Microbiol* 6, 431-440.
- Achtman, M., Zurth, K., Morelli, G., Torrea, G., Guiyoule, A., and Carniel, E. (1999). *Yersinia pestis*, the cause of plague, is a recently emerged clone of *Yersinia pseudotuberculosis*. *Proc Natl Acad Sci U S A* 96, 14043-14048.
- Akerlund, T., Persson, I., Unemo, M., Noren, T., Svenungsson, B., Wullt, M., and Burman, L.G. (2008). Increased sporulation rate of epidemic *Clostridium difficile* Type 027/NAP1. *J Clin Microbiol* 46, 1530-1533.
- al Saif, N., and Brazier, J.S. (1996). The distribution of *Clostridium difficile* in the environment of South Wales. *Journal of medical microbiology* 45, 133-137.
- Albrecht, M., Sharma, C.M., Reinhardt, R., Vogel, J., and Rudel, T. (2010). Deep sequencing-based discovery of the *Chlamydia trachomatis* transcriptome. *Nucleic Acids Res* 38, 868-877.
- Alfa, M.J., Kabani, A., Lysterly, D., Moncrief, S., Neville, L.M., Al-Barrak, A., Harding, G.K., Dyck, B., Olekson, K., and Embil, J.M. (2000). Characterization of a toxin A-negative, toxin B-positive strain of *Clostridium difficile* responsible for a nosocomial outbreak of *Clostridium difficile*-associated diarrhea. *J Clin Microbiol* 38, 2706-2714.
- Assefa, S., Keane, T.M., Otto, T.D., Newbold, C., and Berriman, M. (2009). ABACAS: algorithm-based automatic contiguation of assembled sequences. *Bioinformatics* 25, 1968-1969.
- Aury, J.M., Cruaud, C., Barbe, V., Rogier, O., Mangenot, S., Samson, G., Poulain, J., Anthouard, V., Scarpelli, C., Artiguenave, F., *et al.* (2008). High quality draft sequences for

prokaryotic genomes using a mix of new sequencing technologies. *BMC Genomics* 9, 603.

Bakken, J.S. (2009). Fecal bacteriotherapy for recurrent *Clostridium difficile* infection. *Anaerobe* 15, 285-289.

Barbut, F., and Petit, J.C. (2001). Epidemiology of *Clostridium difficile*-associated infections. *Clin Microbiol Infect* 7, 405-410.

Barrick, J.E., and Lenski, R.E. (2009). Genome-wide mutational diversity in an evolving population of *Escherichia coli*. *Cold Spring Harb Symp Quant Biol* 74, 119-129.

Barrick, J.E., Yu, D.S., Yoon, S.H., Jeong, H., Oh, T.K., Schneider, D., Lenski, R.E., and Kim, J.F. (2009). Genome evolution and adaptation in a long-term experiment with *Escherichia coli*. *Nature* 461, 1243-1247.

Bartlett, J.G. (1994). *Clostridium difficile*: history of its role as an enteric pathogen and the current state of knowledge about the organism. *Clin Infect Dis* 18 Suppl 4, S265-272.

Bartlett, J.G. (2006). Narrative review: the new epidemic of *Clostridium difficile*-associated enteric disease. *Ann Intern Med* 145, 758-764.

Bartlett, J.G. (2008). Historical perspectives on studies of *Clostridium difficile* and *C. difficile* infection. *Clin Infect Dis* 46 Suppl 1, S4-11.

Bartlett, J.G. (2010). *Clostridium difficile*: progress and challenges. *Ann N Y Acad Sci* 1213, 62-69.

Bartlett, J.G., Chang, T.W., Gurwith, M., Gorbach, S.L., and Onderdonk, A.B. (1978). Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. *N Engl J Med* 298, 531-534.

Bartlett, J.G., and Gerding, D.N. (2008). Clinical recognition and diagnosis of *Clostridium difficile* infection. *Clin Infect Dis* 46 Suppl 1, S12-18.

Bartlett, J.G., and Perl, T.M. (2005). The new *Clostridium difficile*--what does it mean? *N Engl J Med* 353, 2503-2505.

Bauer, M.P., Notermans, D.W., van Benthem, B.H., Brazier, J.S., Wilcox, M.H., Rupnik, M., Monnet, D.L., van Dissel, J.T., and Kuijper, E.J. (2011). *Clostridium difficile* infection in Europe: a hospital-based survey. *Lancet* 377, 63-73.

Belanger, S.D., Boissinot, M., Clairoux, N., Picard, F.J., and Bergeron, M.G. (2003). Rapid detection of *Clostridium difficile* in feces by real-time PCR. *J Clin Microbiol* 41, 730-734.

Bennett, S. (2004). Solexa ltd. *Pharmacogenomics* 5, 433-438.

- Bentley, D.R., Balasubramanian, S., Swerdlow, H.P., Smith, G.P., Milton, J., Brown, C.G., Hall, K.P., Evers, D.J., Barnes, C.L., and Bignell, H.R. (2008). Accurate whole human genome sequencing using reversible terminator chemistry. *Nature* 456, 53-59.
- Bentley, S.D., and Parkhill, J. (2004). Comparative genomic structure of prokaryotes. *Annu Rev Genet* 38, 771-792.
- Beres, S.B., Carroll, R.K., Shea, P.R., Sitkiewicz, I., Martinez-Gutierrez, J.C., Low, D.E., McGeer, A., Willey, B.M., Green, K., Tyrrell, G.J., *et al.* (2010). Molecular complexity of successive bacterial epidemics deconvoluted by comparative pathogenomics. *Proc Natl Acad Sci U S A* 107, 4371-4376.
- Bernal, A., Ear, U., and Kyrpides, N. (2001). Genomes Online Database (GOLD): a monitor of genome projects world-wide. *Nucleic Acids Res* 29, 126-127.
- Bielawski, J.P., and Yang, Z. (2003). Maximum likelihood methods for detecting adaptive evolution after gene duplication. *J Struct Funct Genomics* 3, 201-212.
- Bignardi, G.E. (1998). Risk factors for *Clostridium difficile* infection. *J Hosp Infect* 40, 1-15.
- Bouakaze, C., Keyser, C., de Martino, S.J., Sougakoff, W., Veziris, N., Dabernat, H., and Ludes, B. (2010). Identification and genotyping of *Mycobacterium tuberculosis* complex species by use of a SNaPshot Minisequencing-based assay. *J Clin Microbiol* 48, 1758-1766.
- Brazier, J.S., Raybould, R., Patel, B., Duckworth, G., Pearson, A., Charlett, A., and Duerden, B.I. (2008). Distribution and antimicrobial susceptibility patterns of *Clostridium difficile* PCR ribotypes in English hospitals, 2007-08. *Euro Surveill* 13.
- Brinkman, F.S., and Parkhill, J. (2008). Population genomics: modeling the new and a renaissance of the old. *Curr Opin Microbiol* 11, 439-441.
- Brochet, M., Rusniok, C., Couve, E., Dramsi, S., Poyart, C., Trieu-Cuot, P., Kunst, F., and Glaser, P. (2008). Shaping a bacterial genome by large chromosomal replacements, the evolutionary history of *Streptococcus agalactiae*. *Proc Natl Acad Sci U S A* 105, 15961-15966.
- Brouwer, M.S.M., Warburton, P.J., Roberts, A.P., Mullany, P., and Allan, E. (2011). Genetic Organisation, Mobility and Predicted Functions of Genes on Integrated, Mobile Genetic Elements in Sequenced Strains of *Clostridium difficile*. *PLoS ONE* 6, e23014.

- Burdon, D.W., George, R.H., Mogg, G.A., Arabi, Y., Thompson, H., Johnson, M., Alexander-Williams, J., and Keighley, M.R. (1981). Faecal toxin and severity of antibiotic-associated pseudomembranous colitis. *J Clin Pathol* 34, 548-551.
- Burns, D.A., Heap, J.T., and Minton, N.P. (2010). The diverse sporulation characteristics of *Clostridium difficile* clinical isolates are not associated with type. *Anaerobe* 16, 618-622.
- Butler, J., MacCallum, I., Kleber, M., Shlyakhter, I.A., Belmonte, M.K., Lander, E.S., Nusbaum, C., and Jaffe, D.B. (2008). ALLPATHS: de novo assembly of whole-genome shotgun microreads. *Genome Res* 18, 810-820.
- Calabi, E., Ward, S., Wren, B., Paxton, T., Panico, M., Morris, H., Dell, A., Dougan, G., and Fairweather, N. (2001). Molecular characterization of the surface layer proteins from *Clostridium difficile*. *Molecular Microbiology* 40, 1187-1199.
- Campbell, P.J., Stephens, P.J., Pleasance, E.D., O'Meara, S., Li, H., Santarius, T., Stebbings, L.A., Leroy, C., Edkins, S., Hardy, C., *et al.* (2008). Identification of somatically acquired rearrangements in cancer using genome-wide massively parallel paired-end sequencing. *Nat Genet* 40, 722-729.
- Carter, G.P., Awad, M.M., Kelly, M.L., Rood, J.I., and Lyras, D. (2011). TcdB or not TcdB: a tale of two *Clostridium difficile* toxins. *Future Microbiol* 6, 121-123.
- Carter, G.P., Rood, J.I., and Lyras, D. (2010). The role of toxin A and toxin B in *Clostridium difficile*-associated disease: Past and present perspectives. *Gut Microbes* 1, 58-64.
- Carver, T.J., Rutherford, K.M., Berriman, M., Rajandream, M.A., Barrell, B.G., and Parkhill, J. (2005). ACT: the Artemis Comparison Tool. *Bioinformatics* 21, 3422-3423.
- Caugant, D.A., Mocca, L.F., Frasch, C.E., Froholm, L.O., Zollinger, W.D., and Selander, R.K. (1987). Genetic structure of *Neisseria meningitidis* populations in relation to serogroup, serotype, and outer membrane protein pattern. *J Bacteriol* 169, 2781-2792.
- Chain, P.S., Grafham, D.V., Fulton, R.S., Fitzgerald, M.G., Hostetler, J., Muzny, D., Ali, J., Birren, B., Bruce, D.C., Buhay, C., *et al.* (2009). Genomics. Genome project standards in a new era of sequencing. *Science* 326, 236-237.
- Chaisson, M.J., and Pevzner, P.A. (2008). Short read fragment assembly of bacterial genomes. *Genome Res* 18, 324-330.
- Cheknis, A.K., Sambol, S.P., Davidson, D.M., Nagaro, K.J., Mancini, M.C., Hidalgo-Arroyo, G.A., Brazier, J.S., Johnson, S., and Gerding, D.N. (2009). Distribution of *Clostridium*

difficile strains from a North American, European and Australian trial of treatment for *C. difficile* infections: 2005-2007. *Anaerobe* 15, 230-233.

Chernak, E. (2005). Severe *Clostridium difficile*-associated disease in populations previously at low risk — four states. *Morb Mortal Wkly Rep* 54, 1201-1205.

Christensen, S.K., and Gerdes, K. (2003). RelE toxins from bacteria and Archaea cleave mRNAs on translating ribosomes, which are rescued by tmRNA. *Mol Microbiol* 48, 1389-1400.

Cohen, S.H., Tang, Y.J., and Silva, J., Jr. (2001). Molecular typing methods for the epidemiological identification of *Clostridium difficile* strains. *Expert Rev Mol Diagn* 1, 61-70.

Cole, J.R., Wang, Q., Cardenas, E., Fish, J., Chai, B., Farris, R.J., Kulam-Syed-Mohideen, A.S., McGarrell, D.M., Marsh, T., Garrity, G.M., *et al.* (2009). The Ribosomal Database Project: improved alignments and new tools for rRNA analysis. *Nucleic Acids Res* 37, D141-145.

Collins, M.D., Lawson, P.A., Willems, A., Cordoba, J.J., Fernandez-Garayzabal, J., Garcia, P., Cai, J., Hippe, H., and Farrow, J.A. (1994). The phylogeny of the genus *Clostridium*: proposal of five new genera and eleven new species combinations. *Int J Syst Bacteriol* 44, 812-826.

Croucher, N.J., Fookes, M.C., Perkins, T.T., Turner, D.J., Marguerat, S.B., Keane, T., Quail, M.A., He, M., Assefa, S., Bahler, J., *et al.* (2009). A simple method for directional transcriptome sequencing using Illumina technology. *Nucleic Acids Res* 37, e148.

Croucher, N.J., Harris, S.R., Fraser, C., Quail, M.A., Burton, J., van der Linden, M., McGee, L., von Gottberg, A., Song, J.H., Ko, K.S., *et al.* (2011). Rapid pneumococcal evolution in response to clinical interventions. *Science* 331, 430-434.

Dallal, R.M., Harbrecht, B.G., Boujoukas, A.J., Sirio, C.A., Farkas, L.M., Lee, K.K., and Simmons, R.L. (2002). Fulminant *Clostridium difficile*: an underappreciated and increasing cause of death and complications. *Ann Surg* 235, 363-372.

Darling, A.E., Mau, B., and Perna, N.T. (2010). progressiveMauve: multiple genome alignment with gene gain, loss and rearrangement. *PLoS ONE* 5, e11147.

Daubin, V., and Ochman, H. (2004). Bacterial genomes as new gene homes: the genealogy of ORFans in *E. coli*. *Genome Res* 14, 1036-1042.

Delcher, A.L., Harmon, D., Kasif, S., White, O., and Salzberg, S.L. (1999). Improved microbial gene identification with GLIMMER. *Nucleic Acids Res* 27, 4636-4641.

- Dethlefsen, L., McFall-Ngai, M., and Relman, D.A. (2007). An ecological and evolutionary perspective on human-microbe mutualism and disease. *Nature* 449, 811-818.
- Didelot, X., Achtman, M., Parkhill, J., Thomson, N.R., and Falush, D. (2007). A bimodal pattern of relatedness between the *Salmonella* Paratyphi A and Typhi genomes: convergence or divergence by homologous recombination? *Genome Res* 17, 61-68.
- Didelot, X., and Falush, D. (2007). Inference of bacterial microevolution using multilocus sequence data. *Genetics* 175, 1251-1266.
- Didelot, X., and Maiden, M.C. (2010). Impact of recombination on bacterial evolution. *Trends Microbiol* 18, 315-322.
- Ding, F., Tang, P., Hsu, M.H., Cui, P., Hu, S., Yu, J., and Chiu, C.H. (2009). Genome evolution driven by host adaptations results in a more virulent and antimicrobial-resistant *Streptococcus pneumoniae* serotype 14. *BMC Genomics* 10, 158.
- Dingle, K.E., Griffiths, D., Didelot, X., Evans, J., Vaughan, A., Kachrimanidou, M., Stoesser, N., Jolley, K.A., Golubchik, T., Harding, R.M., *et al.* (2011). Clinical *Clostridium difficile*: Clonality and Pathogenicity Locus Diversity. *PLoS ONE* 6, e19993.
- Dobrindt, U., Hochhut, B., Hentschel, U., and Hacker, J. (2004). Genomic islands in pathogenic and environmental microorganisms. *Nat Rev Microbiol* 2, 414-424.
- Dohm, J.C., Lottaz, C., Borodina, T., and Himmelbauer, H. (2008). Substantial biases in ultra-short read data sets from high-throughput DNA sequencing. *Nucleic Acids Res* 36, e105.
- Donati, C., Hiller, N.L., Tettelin, H., Muzzi, A., Croucher, N.J., Angiuoli, S.V., Oggioni, M., Dunning Hotopp, J.C., Hu, F.Z., Riley, D.R., *et al.* (2010). Structure and dynamics of the pan-genome of *Streptococcus pneumoniae* and closely related species. *Genome Biol* 11, R107.
- Doolittle, W.F. (1999). Phylogenetic classification and the universal tree. *Science* 284, 2124-2129.
- Doolittle, W.F., and Papke, R.T. (2006). Genomics and the bacterial species problem. *Genome Biol* 7, 116.
- Dridi, L., Tankovic, J., Burghoffer, B., Barbut, F., and Petit, J.C. (2002). *gyrA* and *gyrB* mutations are implicated in cross-resistance to Ciprofloxacin and moxifloxacin in *Clostridium difficile*. *Antimicrob Agents Chemother* 46, 3418-3421.

- Drudy, D., Fanning, S., and Kyne, L. (2007a). Toxin A-negative, toxin B-positive *Clostridium difficile*. *Int J Infect Dis* 11, 5-10.
- Drudy, D., Harnedy, N., Fanning, S., Hannan, M., and Kyne, L. (2007b). Emergence and control of fluoroquinolone-resistant, toxin A-negative, toxin B-positive *Clostridium difficile*. *Infect Control Hosp Epidemiol* 28, 932-940.
- Drummond, A.J., and Rambaut, A. (2007). BEAST: Bayesian evolutionary analysis by sampling trees. *BMC Evol Biol* 7, 214.
- Drummond, A.J., Rambaut, A., Shapiro, B., and Pybus, O.G. (2005). Bayesian coalescent inference of past population dynamics from molecular sequences. *Mol Biol Evol* 22, 1185-1192.
- Duerden, B.I. (2010). Contribution of a government target to controlling *Clostridium difficile* in the NHS in England. *Anaerobe*.
- Dupuy, B., and Sonenshein, A.L. (1998). Regulated transcription of *Clostridium difficile* toxin genes. *Mol Microbiol* 27, 107-120.
- Endo, T., Ikeo, K., and Gojobori, T. (1996). Large-scale search for genes on which positive selection may operate. *Mol Biol Evol* 13, 685-690.
- Ewing, B., and Green, P. (1998). Base-calling of automated sequencer traces using phred. II. Error probabilities. *Genome Res* 8, 186-194.
- Ewing, B., Hillier, L., Wendl, M.C., and Green, P. (1998). Base-calling of automated sequencer traces using phred. I. Accuracy assessment. *Genome Res* 8, 175-185.
- Fagan, R.P., Albesa-Jove, D., Qazi, O., Svergun, D.I., Brown, K.A., and Fairweather, N.F. (2009). Structural insights into the molecular organization of the S-layer from *Clostridium difficile*. *Mol Microbiol* 71, 1308-1322.
- Falush, D. (2009). Toward the use of genomics to study microevolutionary change in bacteria. *PLoS Genet* 5, e1000627.
- Falush, D., and Bowden, R. (2006). Genome-wide association mapping in bacteria? *Trends Microbiol* 14, 353-355.
- Falush, D., Kraft, C., Taylor, N.S., Correa, P., Fox, J.G., Achtman, M., and Suerbaum, S. (2001). Recombination and mutation during long-term gastric colonization by *Helicobacter pylori*: estimates of clock rates, recombination size, and minimal age. *Proc Natl Acad Sci U S A* 98, 15056-15061.

Falush, D., Torpdahl, M., Didelot, X., Conrad, D.F., Wilson, D.J., and Achtman, M. (2006). Mismatch induced speciation in *Salmonella*: model and data. *Philos Trans R Soc Lond B Biol Sci* 361, 2045-2053.

Fawley, W.N., Underwood, S., Freeman, J., Baines, S.D., Saxton, K., Stephenson, K., Owens, R.C., Jr., and Wilcox, M.H. (2007). Efficacy of hospital cleaning agents and germicides against epidemic *Clostridium difficile* strains. *Infect Control Hosp Epidemiol* 28, 920-925.

Feil, E.J., Cooper, J.E., Grundmann, H., Robinson, D.A., Enright, M.C., Berendt, T., Peacock, S.J., Smith, J.M., Murphy, M., Spratt, B.G., *et al.* (2003). How clonal is *Staphylococcus aureus*? *J Bacteriol* 185, 3307-3316.

Feil, E.J., Enright, M.C., and Spratt, B.G. (2000). Estimating the relative contributions of mutation and recombination to clonal diversification: a comparison between *Neisseria meningitidis* and *Streptococcus pneumoniae*. *Res Microbiol* 151, 465-469.

Feil, E.J., Holmes, E.C., Bessen, D.E., Chan, M.S., Day, N.P., Enright, M.C., Goldstein, R., Hood, D.W., Kalia, A., Moore, C.E., *et al.* (2001). Recombination within natural populations of pathogenic bacteria: short-term empirical estimates and long-term phylogenetic consequences. *Proc Natl Acad Sci U S A* 98, 182-187.

Feil, E.J., Li, B.C., Aanensen, D.M., Hanage, W.P., and Spratt, B.G. (2004). eBURST: inferring patterns of evolutionary descent among clusters of related bacterial genotypes from multilocus sequence typing data. *J Bacteriol* 186, 1518-1530.

Feil, E.J., and Spratt, B.G. (2001). Recombination and the population structures of bacterial pathogens. *Annu Rev Microbiol* 55, 561-590.

Finn, R.D., Tate, J., Mistry, J., Coghill, P.C., Sammut, S.J., Hotz, H.R., Ceric, G., Forslund, K., Eddy, S.R., Sonnhammer, E.L., *et al.* (2008). The Pfam protein families database. *Nucleic Acids Res* 36, D281-288.

Fleischmann, R.D., Adams, M.D., White, O., Clayton, R.A., Kirkness, E.F., Kerlavage, A.R., Bult, C.J., Tomb, J.F., Dougherty, B.A., Merrick, J.M., *et al.* (1995). Whole-genome random sequencing and assembly of *Haemophilus influenzae* Rd. *Science* 269, 496-512.

Fletcher, W., and Yang, Z. (2009). INDELible: a flexible simulator of biological sequence evolution. *Mol Biol Evol* 26, 1879-1888.

Fraser, C., Alm, E.J., Polz, M.F., Spratt, B.G., and Hanage, W.P. (2009). The bacterial species challenge: making sense of genetic and ecological diversity. *Science* 323, 741-746.

Fraser, C., Hanage, W.P., and Spratt, B.G. (2007). Recombination and the nature of bacterial speciation. *Science* 315, 476-480.

- Fraser-Liggett, C.M. (2005). Insights on biology and evolution from microbial genome sequencing. *Genome Res* 15, 1603-1610.
- Gagneux, S., Long, C.D., Small, P.M., Van, T., Schoolnik, G.K., and Bohannan, B.J. (2006). The competitive cost of antibiotic resistance in *Mycobacterium tuberculosis*. *Science* 312, 1944-1946.
- Gawronski, J.D., Wong, S.M., Giannoukos, G., Ward, D.V., and Akerley, B.J. (2009). Tracking insertion mutants within libraries by deep sequencing and a genome-wide screen for *Haemophilus* genes required in the lung. *Proc Natl Acad Sci U S A* 106, 16422-16427.
- George, W.L., Rolfe, R.D., Harding, G.K., Klein, R., Putnam, C.W., and Finegold, S.M. (1982). *Clostridium difficile* and cytotoxin in feces of patients with antimicrobial agent-associated pseudomembranous colitis. *Infection* 10, 205-208.
- Gerding, D.N., Muto, C.A., and Owens, R.C., Jr. (2008). Measures to control and prevent *Clostridium difficile* infection. *Clin Infect Dis* 46 Suppl 1, S43-49.
- Gibbons, R.J., and Kapsimalis, B. (1967). Estimates of the overall rate of growth of the intestinal microflora of hamsters, guinea pigs, and mice. *J Bacteriol* 93, 510-512.
- Gill, S.R., Pop, M., Deboy, R.T., Eckburg, P.B., Turnbaugh, P.J., Samuel, B.S., Gordon, J.I., Relman, D.A., Fraser-Liggett, C.M., and Nelson, K.E. (2006). Metagenomic analysis of the human distal gut microbiome. *Science* 312, 1355-1359.
- Gogarten, J.P., and Townsend, J.P. (2005). Horizontal gene transfer, genome innovation and evolution. *Nat Rev Microbiol* 3, 679-687.
- Goldberg, S.M., Johnson, J., Busam, D., Feldblyum, T., Ferriera, S., Friedman, R., Halpern, A., Khouri, H., Kravitz, S.A., Lauro, F.M., *et al.* (2006). A Sanger/pyrosequencing hybrid approach for the generation of high-quality draft assemblies of marine microbial genomes. *Proc Natl Acad Sci U S A* 103, 11240-11245.
- Goorhuis, A., Bakker, D., Corver, J., Debast, S.B., Harmanus, C., Notermans, D.W., Bergwerff, A.A., Dekker, F.W., and Kuijper, E.J. (2008). Emergence of *Clostridium difficile* infection due to a new hypervirulent strain, polymerase chain reaction ribotype 078. *Clin Infect Dis* 47, 1162-1170.
- Gordon, D., Desmarais, C., and Green, P. (2001). Automated finishing with autofinish. *Genome Res* 11, 614-625.
- Govoni, G., and Gros, P. (1998). Macrophage NRAMP1 and its role in resistance to microbial infections. *Inflamm Res* 47, 277-284.

- Griffiths, D., Fawley, W., Kachrimanidou, M., Bowden, R., Crook, D.W., Fung, R., Golubchik, T., Harding, R.M., Jeffery, K.J., Jolley, K.A., *et al.* (2009). Multilocus Sequence Typing of *Clostridium difficile*. *J Clin Microbiol*.
- Guindon, S., Dufayard, J.F., Lefort, V., Anisimova, M., Hordijk, W., and Gascuel, O. (2010). New algorithms and methods to estimate maximum-likelihood phylogenies: assessing the performance of PhyML 3.0. *Syst Biol* 59, 307-321.
- Guindon, S., and Gascuel, O. (2003). A simple, fast, and accurate algorithm to estimate large phylogenies by maximum likelihood. *Syst Biol* 52, 696-704.
- Gupta, R., Nagarajan, A., and Wajapeyee, N. (2010). Advances in genome-wide DNA methylation analysis. *Biotechniques* 49, iii-xi.
- Gupta, S., and Maiden, M.C. (2001). Exploring the evolution of diversity in pathogen populations. *Trends Microbiol* 9, 181-185.
- Guttman, D.S., and Dykhuizen, D.E. (1994). Clonal divergence in *Escherichia coli* as a result of recombination, not mutation. *Science* 266, 1380-1383.
- Hall, I.C., and O'Toole, E. (1935). Intestinal flora in new-born infants: with a description of a new pathogenic anaerobe, *Bacillus difficilis*. *Archives of Pediatrics and Adolescent Medicine* 49, 390.
- Hanage, W.P., Fraser, C., and Spratt, B.G. (2005). Fuzzy species among recombinogenic bacteria. *BMC Biol* 3, 6.
- Hanage, W.P., Fraser, C., and Spratt, B.G. (2006). Sequences, sequence clusters and bacterial species. *Philos Trans R Soc Lond B Biol Sci* 361, 1917-1927.
- Hanage, W.P., Fraser, C., Tang, J., Connor, T.R., and Corander, J. (2009). Hyper-recombination, diversity, and antibiotic resistance in pneumococcus. *Science* 324, 1454-1457.
- Handelsman, J. (2004). Metagenomics: application of genomics to uncultured microorganisms. *Microbiol Mol Biol Rev* 68, 669-685.
- Harismendy, O., Ng, P.C., Strausberg, R.L., Wang, X., Stockwell, T.B., Beeson, K.Y., Schork, N.J., Murray, S.S., Topol, E.J., Levy, S., *et al.* (2009). Evaluation of next generation sequencing platforms for population targeted sequencing studies. *Genome Biol* 10, R32.
- Harris, S.R., Feil, E.J., Holden, M.T., Quail, M.A., Nickerson, E.K., Chantratita, N., Gardete, S., Tavares, A., Day, N., Lindsay, J.A., *et al.* (2010). Evolution of MRSA during hospital transmission and intercontinental spread. *Science* 327, 469-474.

Hatt, J.K., and Youngman, P. (2000). Mutational analysis of conserved residues in the putative DNA-binding domain of the response regulator Spo0A of *Bacillus subtilis*. J Bacteriol 182, 6975-6982.

Hayes, F. (1998). A family of stability determinants in pathogenic bacteria. J Bacteriol 180, 6415-6418.

Hernandez, D., Francois, P., Farinelli, L., Osteras, M., and Schrenzel, J. (2008). De novo bacterial genome sequencing: millions of very short reads assembled on a desktop computer. Genome Res 18, 802-809.

Hiller, N.L., Janto, B., Hogg, J.S., Boissy, R., Yu, S., Powell, E., Keefe, R., Ehrlich, N.E., Shen, K., Hayes, J., *et al.* (2007). Comparative genomic analyses of seventeen *Streptococcus pneumoniae* strains: insights into the pneumococcal supragenome. J Bacteriol 189, 8186-8195.

Hogg, J.S., Hu, F.Z., Janto, B., Boissy, R., Hayes, J., Keefe, R., Post, J.C., and Ehrlich, G.D. (2007). Characterization and modeling of the *Haemophilus influenzae* core and supragenomes based on the complete genomic sequences of Rd and 12 clinical nontypeable strains. Genome Biol 8, R103.

Holmes, E.C., Urwin, R., and Maiden, M.C. (1999). The influence of recombination on the population structure and evolution of the human pathogen *Neisseria meningitidis*. Mol Biol Evol 16, 741-749.

Holt, K.E., Baker, S., Dongol, S., Basnyat, B., Adhikari, N., Thorson, S., Pulickal, A.S., Song, Y., Parkhill, J., Farrar, J.J., *et al.* (2010). High-throughput bacterial SNP typing identifies distinct clusters of *Salmonella* Typhi causing typhoid in Nepalese children. BMC Infect Dis 10, 144.

Holt, K.E., Parkhill, J., Mazzoni, C.J., Roumagnac, P., Weill, F.X., Goodhead, I., Rance, R., Baker, S., Maskell, D.J., Wain, J., *et al.* (2008). High-throughput sequencing provides insights into genome variation and evolution in *Salmonella* Typhi. Nat Genet 40, 987-993.

Horner, D.S., Pavesi, G., Castrignano, T., De Meo, P.D., Liuni, S., Sammeth, M., Picardi, E., and Pesole, G. (2010). Bioinformatics approaches for genomics and post genomics applications of next-generation sequencing. Brief Bioinform 11, 181-197.

Huang, H., Fang, H., Weintraub, A., and Nord, C.E. (2009). Distinct ribotypes and rates of antimicrobial drug resistance in *Clostridium difficile* from Shanghai and Stockholm. Clin Microbiol Infect.

- Hubert, B., Loo, V.G., Bourgault, A.M., Poirier, L., Dascal, A., Fortin, E., Dionne, M., and Lorange, M. (2007). A portrait of the geographic dissemination of the *Clostridium difficile* North American pulsed-field type 1 strain and the epidemiology of *C. difficile*-associated disease in Quebec. *Clin Infect Dis* 44, 238-244.
- Huse, S.M., Huber, J.A., Morrison, H.G., Sogin, M.L., and Welch, D.M. (2007). Accuracy and quality of massively parallel DNA pyrosequencing. *Genome Biol* 8, R143.
- Huson, D.H., and Bryant, D. (2006). Application of phylogenetic networks in evolutionary studies. *Mol Biol Evol* 23, 254-267.
- Hutchison, C.A., 3rd (2007). DNA sequencing: bench to bedside and beyond. *Nucleic Acids Res* 35, 6227-6237.
- Jain, R., Rivera, M.C., and Lake, J.A. (1999). Horizontal gene transfer among genomes: the complexity hypothesis. *Proc Natl Acad Sci U S A* 96, 3801-3806.
- Janvilisri, T., Scaria, J., Thompson, A.D., Nicholson, A., Limbago, B.M., Arroyo, L.G., Songer, J.G., Grohn, Y.T., and Chang, Y.F. (2009). Microarray identification of *Clostridium difficile* core components and divergent regions associated with host origin. *J Bacteriol* 191, 3881-3891.
- Jasni, A.S., Mullany, P., Hussain, H., and Roberts, A.P. (2010). Demonstration of conjugative transposon (Tn5397)-mediated horizontal gene transfer between *Clostridium difficile* and *Enterococcus faecalis*. *Antimicrob Agents Chemother* 54, 4924-4926.
- Jobstl, M., Heuberger, S., Indra, A., Nepf, R., Kofer, J., and Wagner, M. (2010). *Clostridium difficile* in raw products of animal origin. *Int J Food Microbiol* 138, 172-175.
- Johnson, S. (2009). Recurrent *Clostridium difficile* infection: a review of risk factors, treatments, and outcomes. *J Infect* 58, 403-410.
- Johnson, S., Adelman, A., Clabots, C.R., Peterson, L.R., and Gerding, D.N. (1989). Recurrences of *Clostridium difficile* diarrhea not caused by the original infecting organism. *J Infect Dis* 159, 340-343.
- Johnson, S., Kent, S.A., O'Leary, K.J., Merrigan, M.M., Sambol, S.P., Peterson, L.R., and Gerding, D.N. (2001). Fatal pseudomembranous colitis associated with a variant *Clostridium difficile* strain not detected by toxin A immunoassay. *Ann Intern Med* 135, 434-438.
- Johnson, S., Samore, M.H., Farrow, K.A., Killgore, G.E., Tenover, F.C., Lyras, D., Rood, J.I., DeGirolami, P., Baltch, A.L., Rafferty, M.E., *et al.* (1999). Epidemics of diarrhea caused by

a clindamycin-resistant strain of *Clostridium difficile* in four hospitals. N Engl J Med 341, 1645-1651.

Jolley, K.A., Feil, E.J., Chan, M.S., and Maiden, M.C. (2001). Sequence type analysis and recombinational tests (START). Bioinformatics 17, 1230-1231.

Jolley, K.A., Kalmusova, J., Feil, E.J., Gupta, S., Musilek, M., Kriz, P., and Maiden, M.C. (2000). Carried meningococci in the Czech Republic: a diverse recombining population. J Clin Microbiol 38, 4492-4498.

Joseph, R., Demeyer, D., Vanrenterghem, D., van den Berg, R., Kuijper, E., and Delmee, M. (2005). First isolation of *Clostridium difficile* PCR ribotype 027, toxinotype III in Belgium. Euro Surveill 10, E051020 051024.

Jukes, T.H., and Cantor, C.R. (1969). Evolution of protein molecules. Mammalian protein metabolism 3, 21-132.

Kalia, V.C., Mukherjee, T., Bhushan, A., Joshi, J., Shankar, P., and Huma, N. (2011). Analysis of the unexplored features of rrs (16S rDNA) of the Genus *Clostridium*. BMC Genomics 12, 18.

Keessen, E.C., Gaastra, W., and Lipman, L.J. (2011). *Clostridium difficile* infection in humans and animals, differences and similarities. Vet Microbiol.

Keim, P., Kalif, A., Schupp, J., Hill, K., Travis, S.E., Richmond, K., Adair, D.M., Hugh-Jones, M., Kuske, C.R., and Jackson, P. (1997). Molecular evolution and diversity in *Bacillus anthracis* as detected by amplified fragment length polymorphism markers. J Bacteriol 179, 818-824.

Keim, P., and Smith, K.L. (2002). *Bacillus anthracis* evolution and epidemiology. Curr Top Microbiol Immunol 271, 21-32.

Killgore, G., Thompson, A., Johnson, S., Brazier, J., Kuijper, E., Pepin, J., Frost, E.H., Savelkoul, P., Nicholson, B., van den Berg, R.J., et al. (2008). Comparison of seven techniques for typing international epidemic strains of *Clostridium difficile*: restriction endonuclease analysis, pulsed-field gel electrophoresis, PCR-ribotyping, multilocus sequence typing, multilocus variable-number tandem-repeat analysis, amplified fragment length polymorphism, and surface layer protein A gene sequence typing. J Clin Microbiol 46, 431-437.

Kim, H., Lee, Y., Moon, H.W., Lim, C.S., Lee, K., and Chong, Y. (2011). Emergence of *Clostridium difficile* Ribotype 027 in Korea. Korean J Lab Med 31, 191-196.

- Kim, H., Riley, T.V., Kim, M., Kim, C.K., Yong, D., Lee, K., Chong, Y., and Park, J.W. (2008). Increasing prevalence of toxin A-negative, toxin B-positive isolates of *Clostridium difficile* in Korea: impact on laboratory diagnosis. *J Clin Microbiol* 46, 1116-1117.
- Kimura, M. (1983). *The Neutral Theory of Molecular Evolution*. Cambridge University Press.
- Korbel, J.O., Urban, A.E., Affourtit, J.P., Godwin, B., Grubert, F., Simons, J.F., Kim, P.M., Palejev, D., Carriero, N.J., Du, L., *et al.* (2007). Paired-end mapping reveals extensive structural variation in the human genome. *Science* 318, 420-426.
- Koski, L.B., Morton, R.A., and Golding, G.B. (2001). Codon bias and base composition are poor indicators of horizontally transferred genes. *Mol Biol Evol* 18, 404-412.
- Kryazhimskiy, S., and Plotkin, J.B. (2008). The population genetics of dN/dS. *PLoS Genet* 4, e1000304.
- Kuehne, S.A., Cartman, S.T., Heap, J.T., Kelly, M.L., Cockayne, A., and Minton, N.P. (2010). The role of toxin A and toxin B in *Clostridium difficile* infection. *Nature* 467, 711-713.
- Kuijper, E.J., Barbut, F., Brazier, J.S., Kleinkauf, N., Eckmanns, T., Lambert, M.L., Drudy, D., Fitzpatrick, F., Wiuff, C., Brown, D.J., *et al.* (2008). Update of *Clostridium difficile* infection due to PCR ribotype 027 in Europe, 2008. *Euro Surveill* 13.
- Kuijper, E.J., van Dissel, J.T., and Wilcox, M.H. (2007). *Clostridium difficile*: changing epidemiology and new treatment options. *Curr Opin Infect Dis* 20, 376-383.
- Kurtz, S., Choudhuri, J.V., Ohlebusch, E., Schleiermacher, C., Stoye, J., and Giegerich, R. (2001). REPuter: the manifold applications of repeat analysis on a genomic scale. *Nucleic Acids Res* 29, 4633-4642.
- Kurtz, S., Phillippy, A., Delcher, A.L., Smoot, M., Shumway, M., Antonescu, C., and Salzberg, S.L. (2004). Versatile and open software for comparing large genomes. *Genome Biol* 5, R12.
- Langmead, B., Trapnell, C., Pop, M., and Salzberg, S.L. (2009). Ultrafast and memory-efficient alignment of short DNA sequences to the human genome. *Genome Biol* 10, R25.
- Langridge, G.C., Phan, M.D., Turner, D.J., Perkins, T.T., Parts, L., Haase, J., Charles, I., Maskell, D.J., Peters, S.E., Dougan, G., *et al.* (2009). Simultaneous assay of every *Salmonella* Typhi gene using one million transposon mutants. *Genome Res* 19, 2308-2316.

- Laughon, B.E., Viscidi, R.P., Gdovin, S.L., Yolken, R.H., and Bartlett, J.G. (1984). Enzyme immunoassays for detection of *Clostridium difficile* toxins A and B in fecal specimens. *J Infect Dis* 149, 781-788.
- Lawley, T.D., Clare, S., Walker, A.W., Goulding, D., Stabler, R.A., Croucher, N., Mastroeni, P., Scott, P., Raisen, C., Mottram, L., *et al.* (2009). Antibiotic treatment of *Clostridium difficile* carrier mice triggers a supershedder state, spore-mediated transmission, and severe disease in immunocompromised hosts. *Infect Immun* 77, 3661-3669.
- Lawrence, J.G. (2002). Gene transfer in bacteria: speciation without species? *Theor Popul Biol* 61, 449-460.
- Lawrence, J.G. (2006). Evolution of microbial pathogens, Chapter 2 (Wiley-Blackwell).
- Lefebure, T., and Stanhope, M.J. (2007). Evolution of the core and pan-genome of *Streptococcus*: positive selection, recombination, and genome composition. *Genome Biol* 8, R71.
- Lemee, L., Dhalluin, A., Pestel-Caron, M., Lemeland, J.F., and Pons, J.L. (2004). Multilocus sequence typing analysis of human and animal *Clostridium difficile* isolates of various toxigenic types. *J Clin Microbiol* 42, 2609-2617.
- Lemey, P., Rambaut, A., Drummond, A.J., and Suchard, M.A. (2009). Bayesian phylogeography finds its roots. *PLoS Comput Biol* 5, e1000520.
- Levin, B.R. (1981). Periodic selection, infectious gene exchange and the genetic structure of *E. coli* populations. *Genetics* 99, 1-23.
- Lewis, T., Loman, N.J., Bingle, L., Jumaa, P., Weinstock, G.M., Mortiboy, D., and Pallen, M.J. (2010). High-throughput whole-genome sequencing to dissect the epidemiology of *Acinetobacter baumannii* isolates from a hospital outbreak. *J Hosp Infect* 75, 37-41.
- Li, H., and Durbin, R. (2009). Fast and accurate short read alignment with Burrows-Wheeler transform. *Bioinformatics* 25, 1754-1760.
- Li, H., Handsaker, B., Wysoker, A., Fennell, T., Ruan, J., Homer, N., Marth, G., Abecasis, G., and Durbin, R. (2009). The Sequence Alignment/Map format and SAMtools. *Bioinformatics* 25, 2078-2079.
- Li, H., Ruan, J., and Durbin, R. (2008). Mapping short DNA sequencing reads and calling variants using mapping quality scores. *Genome Res* 18, 1851-1858.

Li, R., Zhu, H., Ruan, J., Qian, W., Fang, X., Shi, Z., Li, Y., Li, S., Shan, G., Kristiansen, K., *et al.* (2010). De novo assembly of human genomes with massively parallel short read sequencing. *Genome Res* 20, 265-272.

Linder, J.A., Huang, E.S., Steinman, M.A., Gonzales, R., and Stafford, R.S. (2005). Fluoroquinolone prescribing in the United States: 1995 to 2002. *Am J Med* 118, 259-268.

Lloyd, A.L., Rasko, D.A., and Mobley, H.L. (2007). Defining genomic islands and uropathogen-specific genes in uropathogenic *Escherichia coli*. *J Bacteriol* 189, 3532-3546.

Loo, V.G., Poirier, L., Miller, M.A., Oughton, M., Libman, M.D., Michaud, S., Bourgault, A.M., Nguyen, T., Frenette, C., Kelly, M., *et al.* (2005). A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. *N Engl J Med* 353, 2442-2449.

Louie, T.J., Miller, M.A., Mullane, K.M., Weiss, K., Lentnek, A., Golan, Y., Gorbach, S., Sears, P., and Shue, Y.K. (2011). Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med* 364, 422-431.

Lovett, S.T., Hurley, R.L., Sutera, V.A., Jr., Aubuchon, R.H., and Lebedeva, M.A. (2002). Crossing over between regions of limited homology in *Escherichia coli*. RecA-dependent and RecA-independent pathways. *Genetics* 160, 851-859.

Lyerly, D.M., Saum, K.E., MacDonald, D.K., and Wilkins, T.D. (1985). Effects of *Clostridium difficile* toxins given intragastrically to animals. *Infect Immun* 47, 349-352.

Lyras, D., O'Connor, J.R., Howarth, P.M., Sambol, S.P., Carter, G.P., Phumoonna, T., Poon, R., Adams, V., Vedantam, G., Johnson, S., *et al.* (2009). Toxin B is essential for virulence of *Clostridium difficile*. *Nature* 458, 1176-1179.

MacCannell, D.R., Louie, T.J., Gregson, D.B., Laverdiere, M., Labbe, A.C., Laing, F., and Henwick, S. (2006). Molecular analysis of *Clostridium difficile* PCR ribotype 027 isolates from Eastern and Western Canada. *J Clin Microbiol* 44, 2147-2152.

MacLean, D., Jones, J.D., and Studholme, D.J. (2009). Application of 'next-generation' sequencing technologies to microbial genetics. *Nat Rev Microbiol* 7, 287-296.

Maiden, M.C., Bygraves, J.A., Feil, E., Morelli, G., Russell, J.E., Urwin, R., Zhang, Q., Zhou, J., Zurth, K., Caugant, D.A., *et al.* (1998). Multilocus sequence typing: a portable approach to the identification of clones within populations of pathogenic microorganisms. *Proc Natl Acad Sci U S A* 95, 3140-3145.

- Maiden, M.C., and Urwin, R. (2006). Evolution of microbial pathogens, Chapter 3 (Wiley-Blackwell).
- Majewski, J., Zawadzki, P., Pickerill, P., Cohan, F.M., and Dowson, C.G. (2000). Barriers to genetic exchange between bacterial species: *Streptococcus pneumoniae* transformation. J Bacteriol 182, 1016-1023.
- Mardis, E.R. (2011). A decade's perspective on DNA sequencing technology. Nature 470, 198-203.
- Margulies, M., Egholm, M., Altman, W.E., Attiya, S., Bader, J.S., Bemben, L.A., Berka, J., Braverman, M.S., Chen, Y.J., Chen, Z., *et al.* (2005). Genome sequencing in microfabricated high-density picolitre reactors. Nature 437, 376-380.
- Matamouros, S., England, P., and Dupuy, B. (2007). *Clostridium difficile* toxin expression is inhibited by the novel regulator TcdC. Mol Microbiol 64, 1274-1288.
- Maurelli, A.T. (2007). Black holes, antivirulence genes, and gene inactivation in the evolution of bacterial pathogens. FEMS Microbiol Lett 267, 1-8.
- McDonald, L.C., Killgore, G.E., Thompson, A., Owens, R.C., Jr., Kazakova, S.V., Sambol, S.P., Johnson, S., and Gerding, D.N. (2005). An epidemic, toxin gene-variant strain of *Clostridium difficile*. N Engl J Med 353, 2433-2441.
- Medini, D., Donati, C., Tettelin, H., Masignani, V., and Rappuoli, R. (2005). The microbial pan-genome. Curr Opin Genet Dev 15, 589-594.
- Medini, D., Serruto, D., Parkhill, J., Relman, D.A., Donati, C., Moxon, R., Falkow, S., and Rappuoli, R. (2008). Microbiology in the post-genomic era. Nat Rev Microbiol 6, 419-430.
- Merrigan, M., Venugopal, A., Mallozzi, M., Roxas, B., Viswanathan, V.K., Johnson, S., Gerding, D.N., and Vedantam, G. (2010). Human hypervirulent *Clostridium difficile* strains exhibit increased sporulation as well as robust toxin production. J Bacteriol 192, 4904-4911.
- Metzker, M.L. (2010). Sequencing technologies - the next generation. Nat Rev Genet 11, 31-46.
- Milkman, R. (1997). Recombination and population structure in *Escherichia coli*. Genetics 146, 745-750.
- Miller, J.R., Koren, S., and Sutton, G. (2010). Assembly algorithms for next-generation sequencing data. Genomics 95, 315-327.

- Mogg, G.A., Burdon, D.W., and Keighley, M. (1979). Oral metronidazole in *Clostridium difficile* colitis. *Br Med J* 2, 335.
- Moir, A. (2006). How do spores germinate? *J Appl Microbiol* 101, 526-530.
- Monot, M., Honore, N., Garnier, T., Zidane, N., Sherafi, D., Paniz-Mondolfi, A., Matsuoka, M., Taylor, G.M., Donoghue, H.D., Bouwman, A., *et al.* (2009). Comparative genomic and phylogeographic analysis of *Mycobacterium leprae*. *Nat Genet* 41, 1282-1289.
- Morelli, G., Song, Y., Mazzoni, C.J., Eppinger, M., Roumagnac, P., Wagner, D.M., Feldkamp, M., Kusecek, B., Vogler, A.J., Li, Y., *et al.* (2010). *Yersinia pestis* genome sequencing identifies patterns of global phylogenetic diversity. *Nat Genet*.
- Mullany, P., Wilks, M., Lamb, I., Clayton, C., Wren, B., and Tabaqchali, S. (1990). Genetic analysis of a tetracycline resistance element from *Clostridium difficile* and its conjugal transfer to and from *Bacillus subtilis*. *J Gen Microbiol* 136, 1343-1349.
- Muto, C.A., Pokrywka, M., Shutt, K., Mendelsohn, A.B., Nouri, K., Posey, K., Roberts, T., Croyle, K., Krystofiak, S., Patel-Brown, S., *et al.* (2005). A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. *Infect Control Hosp Epidemiol* 26, 273-280.
- Nagarajan, N., and Pop, M. (2010). Sequencing and genome assembly using next-generation technologies. *Methods Mol Biol* 673, 1-17.
- Nakamura, Y., Itoh, T., Matsuda, H., and Gojobori, T. (2004). Biased biological functions of horizontally transferred genes in prokaryotic genomes. *Nat Genet* 36, 760-766.
- Nei, M., and Gojobori, T. (1986). Simple methods for estimating the numbers of synonymous and nonsynonymous nucleotide substitutions. *Mol Biol Evol* 3, 418-426.
- Ning, Z., Cox, A.J., and Mullikin, J.C. (2001). SSAHA: a fast search method for large DNA databases. *Genome Res* 11, 1725-1729.
- Noren, T., Akerlund, T., Wullt, M., Burman, L.G., and Unemo, M. (2007). Mutations in *fusA* associated with posttherapy fusidic acid resistance in *Clostridium difficile*. *Antimicrob Agents Chemother* 51, 1840-1843.
- Nyc, O., Pituch, H., Matejkova, J., Obuch-Woszczatynski, P., and Kuijper, E.J. (2011). *Clostridium difficile* PCR ribotype 176 in the Czech Republic and Poland. *Lancet* 377, 1407.

- O'Connor, J.R., Johnson, S., and Gerding, D.N. (2009). *Clostridium difficile* infection caused by the epidemic BI/NAP1/027 strain. *Gastroenterology* 136, 1913-1924.
- Ochman, H., Elwyn, S., and Moran, N.A. (1999). Calibrating bacterial evolution. *Proc Natl Acad Sci U S A* 96, 12638-12643.
- O'Connor, J.R., Galang, M.A., Sambol, S.P., Hecht, D.W., Vedantam, G., Gerding, D.N., and Johnson, S. (2008). Rifampin and rifaximin resistance in clinical isolates of *Clostridium difficile*. *Antimicrob Agents Chemother* 52, 2813-2817.
- O'Connor, J.R., Johnson, S., and Gerding, D.N. (2009). *Clostridium difficile* infection caused by the epidemic BI/NAP1/027 strain. *Gastroenterology* 136, 1913-1924.
- Onderdonk, A.B., Cisneros, R.L., and Bartlett, J.G. (1980). *Clostridium difficile* in gnotobiotic mice. *Infect Immun* 28, 277-282.
- O'Neill, G., Ogunisola, F., Brazier, J., and Duerden, B. (1996). Modification of a PCR Ribotyping Method for Application as a Routine Typing Scheme for *Clostridium difficile*. *Anaerobe* 2, 205-209.
- O'Neill, G.L., Beaman, M.H., and Riley, T.V. (1991). Relapse versus reinfection with *Clostridium difficile*. *Epidemiol Infect* 107, 627-635.
- Pallen, M.J., Loman, N.J., and Penn, C.W. (2010). High-throughput sequencing and clinical microbiology: progress, opportunities and challenges. *Curr Opin Microbiol* 13, 625-631.
- Paredes, C.J., Alsaker, K.V., and Papoutsakis, E.T. (2005). A comparative genomic view of clostridial sporulation and physiology. *Nat Rev Microbiol* 3, 969-978.
- Parkhill, J. (2008). Time to remove the model organism blinkers. *Trends Microbiol* 16, 510-511.
- Peach, S.L., Borriello, S.P., Gaya, H., Barclay, F.E., and Welch, A.R. (1986). Asymptomatic carriage of *Clostridium difficile* in patients with cystic fibrosis. *J Clin Pathol* 39, 1013-1018.
- Pearson, T., Busch, J.D., Ravel, J., Read, T.D., Rhoton, S.D., U'Ren, J.M., Simonson, T.S., Kachur, S.M., Leadem, R.R., Cardon, M.L., *et al.* (2004). Phylogenetic discovery bias in *Bacillus anthracis* using single-nucleotide polymorphisms from whole-genome sequencing. *Proc Natl Acad Sci U S A* 101, 13536-13541.
- Pearson, W.R., and Lipman, D.J. (1988). Improved tools for biological sequence comparison. *Proc Natl Acad Sci U S A* 85, 2444-2448.

Pepin, J., Valiquette, L., Alary, M.E., Villemure, P., Pelletier, A., Forget, K., Pepin, K., and Chouinard, D. (2004). *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. *CMAJ* 171, 466-472.

Perez-Losada, M., Browne, E.B., Madsen, A., Wirth, T., Viscidi, R.P., and Crandall, K.A. (2006). Population genetics of microbial pathogens estimated from multilocus sequence typing (MLST) data. *Infect Genet Evol* 6, 97-112.

Perkins, T.T., Kingsley, R.A., Fookes, M.C., Gardner, P.P., James, K.D., Yu, L., Assefa, S.A., He, M., Croucher, N.J., Pickard, D.J., *et al.* (2009). A strand-specific RNA-Seq analysis of the transcriptome of the typhoid bacillus *Salmonella typhi*. *PLoS Genet* 5, e1000569.

Perna, N.T., Plunkett, G., 3rd, Burland, V., Mau, B., Glasner, J.D., Rose, D.J., Mayhew, G.F., Evans, P.S., Gregor, J., Kirkpatrick, H.A., *et al.* (2001). Genome sequence of enterohaemorrhagic *Escherichia coli* O157:H7. *Nature* 409, 529-533.

Peterson, L.R., Manson, R.U., Paule, S.M., Hacek, D.M., Robicsek, A., Thomson, R.B., Jr., and Kaul, K.L. (2007). Detection of toxigenic *Clostridium difficile* in stool samples by real-time polymerase chain reaction for the diagnosis of *C. difficile*-associated diarrhea. *Clin Infect Dis* 45, 1152-1160.

Pinner, E., Gruenheid, S., Raymond, M., and Gros, P. (1997). Functional complementation of the yeast divalent cation transporter family SMF by NRAMP2, a member of the mammalian natural resistance-associated macrophage protein family. *J Biol Chem* 272, 28933-28938.

Pop, M., and Salzberg, S.L. (2008). Bioinformatics challenges of new sequencing technology. *Trends Genet* 24, 142-149.

Popoff, M.R., Rubin, E.J., Gill, D.M., and Boquet, P. (1988). Actin-specific ADP-ribosyltransferase produced by a *Clostridium difficile* strain. *Infect Immun* 56, 2299-2306.

Posada, D. (2008). jModelTest: phylogenetic model averaging. *Molecular Biology and Evolution* 25, 1253.

Quail, M.A., Kozarewa, I., Smith, F., Scally, A., Stephens, P.J., Durbin, R., Swerdlow, H., and Turner, D.J. (2008). A large genome center's improvements to the Illumina sequencing system. *Nat Methods* 5, 1005-1010.

Rathnayake, I.U., Hargreaves, M., and Huygens, F. (2011). Genotyping of *Enterococcus faecalis* and *Enterococcus faecium* isolates by use of a set of eight single nucleotide polymorphisms. *J Clin Microbiol* 49, 367-372.

- Redelings, M.D., Sorvillo, F., and Mascola, L. (2007). Increase in *Clostridium difficile*-related mortality rates, United States, 1999-2004. *Emerg Infect Dis* 13, 1417-1419.
- Redfield, R.J. (2001). Do bacteria have sex? *Nat Rev Genet* 2, 634-639.
- Reid, S.D., Herbelin, C.J., Bumbaugh, A.C., Selander, R.K., and Whittam, T.S. (2000). Parallel evolution of virulence in pathogenic *Escherichia coli*. *Nature* 406, 64-67.
- Richards, M., Knox, J., Elliott, B., Mackin, K., Lyras, D., Waring, L.J., and Riley, T.V. (2011). Severe infection with *Clostridium difficile* PCR ribotype 027 acquired in Melbourne, Australia. *Med J Aust* 194, 369-371.
- Riggs, M.M., Sethi, A.K., Zabarsky, T.F., Eckstein, E.C., Jump, R.L., and Donskey, C.J. (2007). Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic *Clostridium difficile* strains among long-term care facility residents. *Clin Infect Dis* 45, 992-998.
- Roach, J.C., Boysen, C., Wang, K., and Hood, L. (1995). Pairwise end sequencing: a unified approach to genomic mapping and sequencing. *Genomics* 26, 345-353.
- Roberts, A.P., and Mullany, P. (2009). A modular master on the move: the Tn916 family of mobile genetic elements. *Trends Microbiol* 17, 251-258.
- Roberts, A.P., and Mullany, P. (2011). Tn916-like genetic elements: a diverse group of modular mobile elements conferring antibiotic resistance. *FEMS Microbiol Rev*.
- Roberts, M.C., McFarland, L.V., Mullany, P., and Mulligan, M.E. (1994). Characterization of the genetic basis of antibiotic resistance in *Clostridium difficile*. *J Antimicrob Chemother* 33, 419-429.
- Robinson, D.A., and Enright, M.C. (2004). Evolution of *Staphylococcus aureus* by large chromosomal replacements. *J Bacteriol* 186, 1060-1064.
- Rocha, E.P., Smith, J.M., Hurst, L.D., Holden, M.T., Cooper, J.E., Smith, N.H., and Feil, E.J. (2006). Comparisons of dN/dS are time dependent for closely related bacterial genomes. *J Theor Biol* 239, 226-235.
- Roumagnac, P., Weill, F.X., Dolecek, C., Baker, S., Brisse, S., Chinh, N.T., Le, T.A., Acosta, C.J., Farrar, J., Dougan, G., *et al.* (2006). Evolutionary history of *Salmonella typhi*. *Science* 314, 1301-1304.
- Rouphael, N.G., O'Donnell, J.A., Bhatnagar, J., Lewis, F., Polgreen, P.M., Beekmann, S., Guarner, J., Killgore, G.E., Coffman, B., Campbell, J., *et al.* (2008). *Clostridium difficile*-

associated diarrhea: an emerging threat to pregnant women. *Am J Obstet Gynecol* 198, 635 e631-636.

Rubin, E.M., Lucas, S., Richardson, P., Rokhsar, D., and Pennacchio, L. (2004). Finishing the euchromatic sequence of the human genome. *Nature* 431.

Rupnik, M., Avesani, V., Janc, M., von Eichel-Streiber, C., and Delmee, M. (1998). A novel toxinotyping scheme and correlation of toxinotypes with serogroups of *Clostridium difficile* isolates. *J Clin Microbiol* 36, 2240-2247.

Rupnik, M., Wilcox, M.H., and Gerding, D.N. (2009). *Clostridium difficile* infection: new developments in epidemiology and pathogenesis. *Nat Rev Microbiol* 7, 526-536.

Rutherford, K., Parkhill, J., Crook, J., Horsnell, T., Rice, P., Rajandream, M.A., and Barrell, B. (2000). Artemis: sequence visualization and annotation. *Bioinformatics* 16, 944-945.

Sanger, F., Air, G.M., Barrell, B.G., Brown, N.L., Coulson, A.R., Fiddes, C.A., Hutchison, C.A., Slocombe, P.M., and Smith, M. (1977). Nucleotide sequence of bacteriophage phi X174 DNA. *Nature* 265, 687-695.

Sanger, F., and Coulson, A.R. (1975). A rapid method for determining sequences in DNA by primed synthesis with DNA polymerase. *J Mol Biol* 94, 441-448.

Savage, A.M., and Alford, R.H. (1983). Nosocomial spread of *Clostridium difficile*. *Infect Control* 4, 31-33.

Saxton, K., Baines, S.D., Freeman, J., O'Connor, R., and Wilcox, M.H. (2009). Effects of exposure of *Clostridium difficile* PCR ribotypes 027 and 001 to fluoroquinolones in a human gut model. *Antimicrob Agents Chemother* 53, 412-420.

Scaria, J., Ponnala, L., Janvilisri, T., Yan, W., Mueller, L.A., and Chang, Y.F. (2010). Analysis of ultra low genome conservation in *Clostridium difficile*. *PLoS ONE* 5, e15147.

Schmidt, M.L., and Gilligan, P.H. (2009). *Clostridium difficile* testing algorithms: what is practical and feasible? *Anaerobe* 15, 270-273.

Sebahia, M., Wren, B.W., Mullany, P., Fairweather, N.F., Minton, N., Stabler, R., Thomson, N.R., Roberts, A.P., Cerdeno-Tarraga, A.M., Wang, H., *et al.* (2006). The multidrug-resistant human pathogen *Clostridium difficile* has a highly mobile, mosaic genome. *Nat Genet* 38, 779-786.

Sekulovic, O., Meessen-Pinard, M., and Fortier, L.C. (2011). Prophage-stimulated toxin production in *Clostridium difficile* NAP1/027 lysogens. *Journal of Bacteriology* 193, 2726.

- Selander, R.K., and Levin, B.R. (1980). Genetic diversity and structure in *Escherichia coli* populations. *Science* 210, 545-547.
- Setlow, P. (2003). Spore germination. *Curr Opin Microbiol* 6, 550-556.
- Sharma, C.M., Hoffmann, S., Darfeuille, F., Reignier, J., Findeiss, S., Sittka, A., Chabas, S., Reiche, K., Hackermuller, J., Reinhardt, R., *et al.* (2010). The primary transcriptome of the major human pathogen *Helicobacter pylori*. *Nature* 464, 250-255.
- Shendure, J., and Ji, H. (2008). Next-generation DNA sequencing. *Nat Biotechnol* 26, 1135-1145.
- Sheppard, S.K., McCarthy, N.D., Falush, D., and Maiden, M.C. (2008). Convergence of *Campylobacter* species: implications for bacterial evolution. *Science* 320, 237-239.
- Sheridan, P.P., Freeman, K.H., and Brenchley, J.E. (2003). Estimated minimal divergence times of the major bacterial and archaeal phyla. *Geomicrobiology Journal* 20, 1-14.
- Silva, J., Jr., Batts, D.H., Fekety, R., Plouffe, J.F., Rifkin, G.D., and Baird, I. (1981). Treatment of *Clostridium difficile* colitis and diarrhea with vancomycin. *Am J Med* 71, 815-822.
- Skippington, E., and Ragan, M.A. (2011). Lateral genetic transfer and the construction of genetic exchange communities. *FEMS Microbiol Rev.*
- Smith, J.M., Dowson, C.G., and Spratt, B.G. (1991). Localized sex in bacteria. *Nature* 349, 29-31.
- Smith, J.M., Smith, N.H., O'Rourke, M., and Spratt, B.G. (1993). How clonal are bacteria? *Proc Natl Acad Sci U S A* 90, 4384-4388.
- Smith, L.M., Sanders, J.Z., Kaiser, R.J., Hughes, P., Dodd, C., Connell, C.R., Heiner, C., Kent, S.B., and Hood, L.E. (1986). Fluorescence detection in automated DNA sequence analysis. *Nature* 321, 674-679.
- Smith, N.H., Gordon, S.V., de la Rúa-Domenech, R., Clifton-Hadley, R.S., and Hewinson, R.G. (2006). Bottlenecks and broomsticks: the molecular evolution of *Mycobacterium bovis*. *Nat Rev Microbiol* 4, 670-681.
- Songer, J.G., Jones, R., Anderson, M.A., Barbara, A.J., Post, K.W., and Trinh, H.T. (2007). Prevention of porcine *Clostridium difficile*-associated disease by competitive exclusion with nontoxigenic organisms. *Vet Microbiol* 124, 358-361.
- Spigaglia, P., Barbanti, F., Louie, T., Barbut, F., and Mastrantonio, P. (2009). Molecular analysis of the *gyrA* and *gyrB* quinolone resistance-determining regions of

- fluoroquinolone-resistant *Clostridium difficile* mutants selected in vitro. Antimicrob Agents Chemother 53, 2463-2468.
- Spigaglia, P., Barbanti, F., Mastrantonio, P., Brazier, J.S., Barbut, F., Delmee, M., Kuijper, E., and Poxton, I.R. (2008). Fluoroquinolone resistance in *Clostridium difficile* isolates from a prospective study of *C. difficile* infections in Europe. Journal of medical microbiology 57, 784-789.
- Spigaglia, P., Carattoli, A., Barbanti, F., and Mastrantonio, P. (2010). Detection of *gyrA* and *gyrB* mutations in *Clostridium difficile* isolates by real-time PCR. Mol Cell Probes 24, 61-67.
- Spigaglia, P., Carucci, V., Barbanti, F., and Mastrantonio, P. (2005). ErmB determinants and Tn916-Like elements in clinical isolates of *Clostridium difficile*. Antimicrob Agents Chemother 49, 2550-2553.
- Spigaglia, P., and Mastrantonio, P. (2002). Molecular analysis of the pathogenicity locus and polymorphism in the putative negative regulator of toxin production (TcdC) among *Clostridium difficile* clinical isolates. J Clin Microbiol 40, 3470-3475.
- Spratt, B.G. (2004). Exploring the concept of clonality in bacteria. Methods Mol Biol 266, 323-352.
- Spratt, B.G., Hanage, W.P., and Feil, E.J. (2001). The relative contributions of recombination and point mutation to the diversification of bacterial clones. Curr Opin Microbiol 4, 602-606.
- Spratt, B.G., and Maiden, M.C. (1999). Bacterial population genetics, evolution and epidemiology. Philos Trans R Soc Lond B Biol Sci 354, 701-710.
- Sreevatsan, S., Pan, X., Stockbauer, K.E., Connell, N.D., Kreiswirth, B.N., Whittam, T.S., and Musser, J.M. (1997). Restricted structural gene polymorphism in the *Mycobacterium tuberculosis* complex indicates evolutionarily recent global dissemination. Proc Natl Acad Sci U S A 94, 9869-9874.
- Srivatsan, A., Han, Y., Peng, J., Tehranchi, A.K., Gibbs, R., Wang, J.D., and Chen, R. (2008). High-precision, whole-genome sequencing of laboratory strains facilitates genetic studies. PLoS Genet 4, e1000139.
- Stabler, R.A., Gerding, D.N., Songer, J.G., Drudy, D., Brazier, J.S., Trinh, H.T., Witney, A.A., Hinds, J., and Wren, B.W. (2006). Comparative phylogenomics of *Clostridium difficile* reveals clade specificity and microevolution of hypervirulent strains. J Bacteriol 188, 7297-7305.

Stabler, R.A., He, M., Dawson, L., Martin, M., Valiente, E., Corton, C., Lawley, T.D., Sebahia, M., Quail, M.A., Rose, G., *et al.* (2009). Comparative genome and phenotypic analysis of *Clostridium difficile* 027 strains provides insight into the evolution of a hypervirulent bacterium. *Genome Biol* 10, R102.

Stackebrandt, E. Taxonomic parameters revisited: tarnished gold standards. *Microbiology Today* 33, 153-155.

Stamatakis, A. (2006). RAxML-VI-HPC: maximum likelihood-based phylogenetic analyses with thousands of taxa and mixed models. *Bioinformatics* 22, 2688-2690.

Stamper, P.D., Babiker, W., Alcabasa, R., Aird, D., Wehrin, J., Ikpeama, I., Gluck, L., and Carroll, K.C. (2009). Evaluation of a new commercial TaqMan PCR assay for direct detection of the *Clostridium difficile* toxin B gene in clinical stool specimens. *J Clin Microbiol* 47, 3846-3850.

Stubbs, S.L., Brazier, J.S., O'Neill, G.L., and Duerden, B.I. (1999). PCR targeted to the 16S-23S rRNA gene intergenic spacer region of *Clostridium difficile* and construction of a library consisting of 116 different PCR ribotypes. *J Clin Microbiol* 37, 461-463.

Studholme, D.J., Ibanez, S.G., MacLean, D., Dangl, J.L., Chang, J.H., and Rathjen, J.P. (2009). A draft genome sequence and functional screen reveals the repertoire of type III secreted proteins of *Pseudomonas syringae* pathovar tabaci 11528. *BMC Genomics* 10, 395.

Suchard, M.A., Weiss, R.E., and Sinsheimer, J.S. (2001). Bayesian selection of continuous-time Markov chain evolutionary models. *Mol Biol Evol* 18, 1001-1013.

Tanner, H.E., Hardy, K.J., and Hawkey, P.M. (2010). Coexistence of multiple multilocus variable-number tandem-repeat analysis subtypes of *Clostridium difficile* PCR ribotype 027 strains within fecal specimens. *J Clin Microbiol* 48, 985-987.

Taylor, N.S., Thorne, G.M., and Bartlett, J.G. (1981). Comparison of two toxins produced by *Clostridium difficile*. *Infect Immun* 34, 1036-1043.

Teasley, D.G., Gerding, D.N., Olson, M.M., Peterson, L.R., Gebhard, R.L., Schwartz, M.J., and Lee, J.T., Jr. (1983). Prospective randomised trial of metronidazole versus vancomycin for *Clostridium difficile*-associated diarrhoea and colitis. *Lancet* 2, 1043-1046.

Tedesco, F.J., Barton, R.W., and Alpers, D.H. (1974). Clindamycin-associated colitis. A prospective study. *Ann Intern Med* 81, 429-433.

Tettelin, H., and Feldblyum, T. (2009). Bacterial genome sequencing. *Methods Mol Biol* 551, 231-247.

- Tettelin, H., Massignani, V., Cieslewicz, M.J., Donati, C., Medini, D., Ward, N.L., Angiuoli, S.V., Crabtree, J., Jones, A.L., Durkin, A.S., *et al.* (2005). Genome analysis of multiple pathogenic isolates of *Streptococcus agalactiae*: implications for the microbial "pan-genome". *Proc Natl Acad Sci U S A* 102, 13950-13955.
- Thomas, C.M., and Nielsen, K.M. (2005). Mechanisms of, and barriers to, horizontal gene transfer between bacteria. *Nat Rev Microbiol* 3, 711-721.
- Turcatti, G., Romieu, A., Fedurco, M., and Tairi, A.P. (2008). A new class of cleavable fluorescent nucleotides: synthesis and optimization as reversible terminators for DNA sequencing by synthesis. *Nucleic Acids Res* 36, e25.
- Turnbaugh, P.J., Ley, R.E., Mahowald, M.A., Magrini, V., Mardis, E.R., and Gordon, J.I. (2006). An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 444, 1027-1031.
- Tyson, G.W., Chapman, J., Hugenholtz, P., Allen, E.E., Ram, R.J., Richardson, P.M., Solovyev, V.V., Rubin, E.M., Rokhsar, D.S., and Banfield, J.F. (2004). Community structure and metabolism through reconstruction of microbial genomes from the environment. *Nature* 428, 37-43.
- Underwood, S., Guan, S., Vijayasubhash, V., Baines, S.D., Graham, L., Lewis, R.J., Wilcox, M.H., and Stephenson, K. (2009). Characterization of the sporulation initiation pathway of *Clostridium difficile* and its role in toxin production. *J Bacteriol* 191, 7296-7305.
- van den Berg, R.J., Schaap, I., Templeton, K.E., Klaassen, C.H., and Kuijper, E.J. (2007). Typing and subtyping of *Clostridium difficile* isolates by using multiple-locus variable-number tandem-repeat analysis. *J Clin Microbiol* 45, 1024-1028.
- Venter, J.C., Remington, K., Heidelberg, J.F., Halpern, A.L., Rusch, D., Eisen, J.A., Wu, D., Paulsen, I., Nelson, K.E., Nelson, W., *et al.* (2004). Environmental genome shotgun sequencing of the Sargasso Sea. *Science* 304, 66-74.
- Vernikos, G.S., and Parkhill, J. (2006). Interpolated variable order motifs for identification of horizontally acquired DNA: revisiting the *Salmonella* pathogenicity islands. *Bioinformatics* 22, 2196-2203.
- Vogler, A.J., Busch, J.D., Percy-Fine, S., Tipton-Hunton, C., Smith, K.L., and Keim, P. (2002). Molecular analysis of rifampin resistance in *Bacillus anthracis* and *Bacillus cereus*. *Antimicrob Agents Chemother* 46, 511-513.

- Von Abercron, S.M., Karlsson, F., Wigh, G.T., Wierup, M., and Krovacek, K. (2009). Low occurrence of *Clostridium difficile* in retail ground meat in Sweden. *J Food Prot* 72, 1732-1734.
- Vonberg, R.P., Kuijper, E.J., Wilcox, M.H., Barbut, F., Tull, P., Gastmeier, P., van den Broek, P.J., Colville, A., Coignard, B., Daha, T., *et al.* (2008). Infection control measures to limit the spread of *Clostridium difficile*. *Clin Microbiol Infect* 14 Suppl 5, 2-20.
- Vos, M. (2009). Why do bacteria engage in homologous recombination? *Trends Microbiol* 17, 226-232.
- Vos, M., and Didelot, X. (2009). A comparison of homologous recombination rates in bacteria and archaea. *ISME J* 3, 199-208.
- Voth, D.E., and Ballard, J.D. (2005). *Clostridium difficile* toxins: mechanism of action and role in disease. *Clin Microbiol Rev* 18, 247-263.
- Walters, B.A., Roberts, R., Stafford, R., and Seneviratne, E. (1983). Relapse of antibiotic associated colitis: endogenous persistence of *Clostridium difficile* during vancomycin therapy. *Gut* 24, 206-212.
- Wang, H., Roberts, A.P., Lyras, D., Rood, J.I., Wilks, M., and Mullany, P. (2000). Characterization of the ends and target sites of the novel conjugative transposon Tn5397 from *Clostridium difficile*: excision and circularization is mediated by the large resolvase, TndX. *J Bacteriol* 182, 3775-3783.
- Wang, J., Karnati, P.K., Takacs, C.M., Kowalski, J.C., and Derbyshire, K.M. (2005). Chromosomal DNA transfer in *Mycobacterium smegmatis* is mechanistically different from classical Hfr chromosomal DNA transfer. *Mol Microbiol* 58, 280-288.
- Ward, T.J., Ducey, T.F., Usgaard, T., Dunn, K.A., and Bielawski, J.P. (2008). Multilocus genotyping assays for single nucleotide polymorphism-based subtyping of *Listeria monocytogenes* isolates. *Appl Environ Microbiol* 74, 7629-7642.
- Warny, M., Pepin, J., Fang, A., Killgore, G., Thompson, A., Brazier, J., Frost, E., and McDonald, L.C. (2005). Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. *Lancet* 366, 1079-1084.
- Welch, R.A., Burland, V., Plunkett, G., 3rd, Redford, P., Roesch, P., Rasko, D., Buckles, E.L., Liou, S.R., Boutin, A., Hackett, J., *et al.* (2002). Extensive mosaic structure revealed by the complete genome sequence of uropathogenic *Escherichia coli*. *Proc Natl Acad Sci U S A* 99, 17020-17024.

- Wilcox, M.H., Planche, T., Fang, F.C., and Gilligan, P. (2010). What is the current role of algorithmic approaches for diagnosis of *Clostridium difficile* infection? J Clin Microbiol 48, 4347-4353.
- Wirth, T., Falush, D., Lan, R., Colles, F., Mensa, P., Wieler, L.H., Karch, H., Reeves, P.R., Maiden, M.C., Ochman, H., *et al.* (2006). Sex and virulence in *Escherichia coli*: an evolutionary perspective. Mol Microbiol 60, 1136-1151.
- Wozniak, R.A., and Waldor, M.K. (2010). Integrative and conjugative elements: mosaic mobile genetic elements enabling dynamic lateral gene flow. Nat Rev Microbiol 8, 552-563.
- Wren, B.W., and Tabaqchali, S. (1987). Restriction endonuclease DNA analysis of *Clostridium difficile*. J Clin Microbiol 25, 2402-2404.
- Wust, J., Sullivan, N.M., Hardegger, U., and Wilkins, T.D. (1982). Investigation of an outbreak of antibiotic-associated colitis by various typing methods. J Clin Microbiol 16, 1096-1101.
- Yang, Z. (2007). PAML 4: phylogenetic analysis by maximum likelihood. Mol Biol Evol 24, 1586-1591.
- Yang, Z., and Bielawski, J.P. (2000). Statistical methods for detecting molecular adaptation. Trends Ecol Evol 15, 496-503.
- Yoon, S.S., and Brandt, L.J. (2010). Treatment of refractory/recurrent *C. difficile*-associated disease by donated stool transplanted via colonoscopy: a case series of 12 patients. J Clin Gastroenterol 44, 562-566.
- Zar, F.A., Bakkanagari, S.R., Moorthi, K.M., and Davis, M.B. (2007). A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. Clin Infect Dis 45, 302-307.
- Zerbino, D.R., and Birney, E. (2008). Velvet: algorithms for de novo short read assembly using de Bruijn graphs. Genome Res 18, 821-829.