

Bibliography

- 1000 Genomes Project Consortium, Abecasis, G. R., Auton, A., Brooks, L. D., DePristo, M. A., Durbin, R. M., ... McVean, G. A. (2012). An integrated map of genetic variation from 1,092 human genomes. *Nature*, *491*(7422), 56–65.
- 1000 Genomes Project Consortium, Auton, A., Brooks, L. D., Durbin, R. M., Garrison, E. P., Kang, H. M., ... Abecasis, G. R. (2015). A global reference for human genetic variation. *Nature*, *526*(7571), 68–74.
- Abdullahi, O., Karani, A., Tigoi, C. C., Mugo, D., Kungu, S., Wanjiru, E., ... Scott, J. A. G. (2012a). Rates of acquisition and clearance of pneumococcal serotypes in the nasopharynges of children in kilifi district, kenya. *J. Infect. Dis.* *206*(7), 1020–1029.
- Abdullahi, O., Karani, A., Tigoi, C. C., Mugo, D., Kungu, S., Wanjiru, E., ... Scott, J. A. G. (2012b). The prevalence and risk factors for pneumococcal colonization of the nasopharynx among children in kilifi district, kenya. *PLoS One*, *7*(2), e30787.
- Abel, L. & Dessein, A. J. (1997). The impact of host genetics on susceptibility to human infectious diseases. *Curr. Opin. Immunol.* *9*(4), 509–516.
- Abeyta, M., Hardy, G. G. & Yother, J. (2003). Genetic alteration of capsule type but not PspA type affects accessibility of surface-bound complement and surface antigens of streptococcus pneumoniae. *Infect. Immun.* *71*(1), 218–225.
- Adriani, K. S., Brouwer, M. C. & Beek, D. V. D. (2015). Risk factors for community-acquired bacterial meningitis in adults. *Neth. J. Med.* *73*(2), 53–60.
- Afzal, M., Shafeeq, S., Henriques-Normark, B. & Kuipers, O. P. (2015). UlaR activates expression of the ula operon in streptococcus pneumoniae in the presence of ascorbic acid. *Microbiology*, *161*(Pt 1), 41–49.
- Aggarwala, V. & Voight, B. F. (2016). An expanded sequence context model broadly explains variability in polymorphism levels across the human genome. *Nat. Genet.* *48*(4), 349–355.
- Agresti, A. (2015). *Foundations of linear and generalized linear models (wiley series in probability and statistics)* (1 edition). Wiley-Blackwell.
- Akaike, H. (1974). A new look at the statistical model identification. *IEEE Trans. Automat. Contr.* *19*(6), 716–723.

- Alam, M. T., Petit, R. A., 3rd, Crispell, E. K., Thornton, T. A., Conneely, K. N., Jiang, Y., . . . Read, T. D. (2014). Dissecting vancomycin-intermediate resistance in staphylococcus aureus using genome-wide association. *Genome Biol. Evol.* 6(5), 1174–1185.
- Alfonseca, M., Cebrián, M. & Ortega, A. (2005). Common pitfalls using the normalized compression distance: What to watch out for in a compressor. *Commun. Inf. Syst.* 5(4), 367–384.
- Allegrucci, M., Hu, F., Shen, K., Hayes, J., Ehrlich, G. D., Post, J. C. & Sauer, K. (2006). Phenotypic characterization of streptococcus pneumoniae biofilm development. *J. Bacteriol.* 188(7), 2325.
- AlonsoDeVelasco, E., Verheul, A. F., Verhoef, J. & Snippe, H. (1995). Streptococcus pneumoniae: Virulence factors, pathogenesis, and vaccines. *Microbiol. Rev.* 59(4), 591–603.
- Altshuler, D., Daly, M. J. & Lander, E. (2008). Genetic mapping in human disease. *Science*, 322(5903), 881–888.
- Amos, W. & Hoffman, J. I. (2010). Evidence that two main bottleneck events shaped modern human genetic diversity. *Proc. Biol. Sci.* 277(1678), 131–137.
- Anderson, C. A., Pettersson, F. H., Clarke, G. M., Cardon, L. R., Morris, A. P. & Zondervan, K. T. (2010). Data quality control in genetic case-control association studies. *Nat. Protoc.* 5(9), 1564–1573.
- Anderson, T. J. C., Williams, J. T., Nair, S., Sudimack, D., Barends, M., Jaidee, A., . . . Nosten, F. (2010). Inferred relatedness and heritability in malaria parasites. *Proc. Biol. Sci.* 277(1693), 2531–2540.
- André, G. O., Politano, W. R., Mirza, S., Converso, T. R., Ferraz, L. F. C., Leite, L. C. C. & Darrieux, M. (2015). Combined effects of lactoferrin and lysozyme on streptococcus pneumoniae killing. *Microb. Pathog.* 89, 7–17.
- Anttila, M., Voutilainen, M., Jääntti, V., Eskola, J. & Käyhty, H. (1999). Contribution of serotype-specific IgG concentration, IgG subclasses and relative antibody avidity to opsonophagocytic activity against streptococcus pneumoniae. *Clin. Exp. Immunol.* 118(3), 402–407.
- Aronin, S. I., Peduzzi, P. & Quagliarello, V. J. (1998). Community-acquired bacterial meningitis: Risk stratification for adverse clinical outcome and effect of antibiotic timing. *Ann. Intern. Med.* 129(11), 862–869.
- Attia, J., Hatala, R., Cook, D. J. & Wong, J. G. (1999). The rational clinical examination. does this adult patient have acute meningitis? *JAMA*, 282(2), 175–181.
- Auranen, K., Mehtälä, J., Tanskanen, A. & S Kaltoft, M. (2010). Between-strain competition in acquisition and clearance of pneumococcal carriage—epidemiologic evidence from a longitudinal study of day-care children. *Am. J. Epidemiol.* 171(2), 169–176.

- Azim Ansari, M., Pedergnana, V., Ip, C. L. C., Magri, A., Von Delft, A., Bonsall, D., ... Spencer, C. C. A. (2017). Genome-to-genome analysis highlights the effect of the human innate and adaptive immune systems on the hepatitis C virus. *Nat. Genet.*
- Bai, Y., Yang, J., Eisele, L. E., Underwood, A. J., Koestler, B. J., Waters, C. M., ... Bai, G. (2013). Two DHH subfamily 1 proteins in streptococcus pneumoniae possess cyclic Di-AMP phosphodiesterase activity and affect bacterial growth and virulence. *J. Bacteriol.* 195(22), 5123–5132.
- Bainbridge, T. W., DeAlmeida, V. I., Izrael-Tomasevic, A., Chalouni, C., Pan, B., Goldsmith, J., ... Ernst, J. A. (2014). Evolutionary divergence in the catalytic activity of the CAM-1, ROR1 and ROR2 kinase domains. *PLoS One*, 9(7), e102695.
- Balachandran, P., Hollingshead, S. K., Paton, J. C. & Briles, D. E. (2001). The autolytic enzyme LytA of streptococcus pneumoniae is not responsible for releasing pneumolysin. *J. Bacteriol.* 183(10), 3108–3116.
- Balmer, P., North, J., Baxter, D., Stanford, E., Melegaro, A., Kaczmarek, E. B., ... Borrow, R. (2003). Measurement and interpretation of pneumococcal IgG levels for clinical management. *Clin. Exp. Immunol.* 133(3), 364–369.
- Bamshad, M. & Wooding, S. P. (2003). Signatures of natural selection in the human genome. *Nat. Rev. Genet.* 4(2), 99–111.
- Bankevich, A., Nurk, S., Antipov, D., Gurevich, A. a., Dvorkin, M., Kulikov, A. S., ... Pevzner, P. a. (2012). SPAdes: A new genome assembly algorithm and its applications to single-cell sequencing. *J. Comput. Biol.* 19(5), 455–477.
- Barrett, J. C., Buxbaum, J., Cutler, D., Daly, M., Devlin, B., Gratten, J., ... Wray, N. R. (2017). *New mutations, old statistical challenges.*
- Barrick, J. E., Yu, D. S., Yoon, S. H., Jeong, H., Oh, T. K., Schneider, D., ... Kim, J. F. (2009). Genome evolution and adaptation in a long-term experiment with escherichia coli. *Nature*, 461(7268), 1243–1247.
- Bartha, I., Carlson, J. M., Brumme, C. J., McLaren, P. J., Brumme, Z. L., John, M., ... Fellay, J. (2013). A genome-to-genome analysis of associations between human genetic variation, HIV-1 sequence diversity, and viral control. *Elife*, 2, 1–16.
- Bek-Thomsen, M., Poulsen, K. & Kilian, M. (2012). Occurrence and evolution of the paralogous zinc metalloproteases IgA1 protease, ZmpB, ZmpC, and ZmpD in streptococcus pneumoniae and related commensal species. *MBio*, 3(5).
- Bensing, B. A., Siboo, I. R. & Sullam, P. M. (2001). Proteins PblA and PblB of streptococcus mitis, which promote binding to human platelets, are encoded within a lysogenic bacteriophage. *Infect. Immun.* 69(10), 6186–6192.
- Bentley, S. D., Aanensen, D. M., Mavroidi, A., Saunders, D., Rabbinowitsch, E., Collins, M., ... Spratt, B. G. (2006). Genetic analysis of the capsular biosynthetic locus from all 90 pneumococcal serotypes. *PLoS Genet.* 2(3), e31.

- Bentley, S. D. & Parkhill, J. (2004). Comparative genomic structure of prokaryotes. *Annu. Rev. Genet.* 38, 771–792.
- Berry, A. M. & Paton, J. C. (2000). Additive attenuation of virulence of streptococcus pneumoniae by mutation of the genes encoding pneumolysin and other putative pneumococcal virulence proteins. *Infect. Immun.* 68(1), 133–140.
- Bijlsma, M. W., Brouwer, M. C., Kasanmoentalib, E. S., Kloek, A. T., Lucas, M. J., Tanck, M. W., ... van de Beek, D. (2016). Community-acquired bacterial meningitis in adults in the netherlands, 2006–14: A prospective cohort study. *Lancet Infect. Dis.* 16(3), 339–347.
- Bille, E., Ure, R., Gray, S. J., Kaczmarek, E. B., McCarthy, N. D., Nassif, X., ... Tinsley, C. R. (2008). Association of a bacteriophage with meningococcal disease in young adults. *PLoS One*, 3(12), e3885.
- Bille, E., Zahar, J.-R., Perrin, A., Morelle, S., Kriz, P., Jolley, K. A., ... Tinsley, C. R. (2005). A chromosomally integrated bacteriophage in invasive meningococci. *J. Exp. Med.* 201(12), 1905–1913.
- Blanquart, F., Wymant, C., Cornelissen, M., Gall, A., Bakker, M., Bezemer, D., ... BEE-HIVE collaboration. (2017). Viral genetic variation accounts for a third of variability in HIV-1 set-point viral load in europe. *PLoS Biol.* 15(6), e2001855.
- Bogaardt, C., van Tonder, A. J. & Brueggemann, A. B. (2015). Genomic analyses of pneumococci reveal a wide diversity of bacteriocins - including pneumocyclicin, a novel circular bacteriocin. *BMC Genomics*, 16, 554.
- Bogaert, D., van Belkum, A., Sluijter, M., Luijendijk, A., de Groot, R., Rümke, H. C., ... Hermans, P. W. M. (2004). Colonisation by streptococcus pneumoniae and staphylococcus aureus in healthy children. *Lancet*, 363(9424), 1871–1872.
- Bohr, V., Rasmussen, N., Hansen, B., Kjersem, H., Jessen, O., Johnsen, N. & Kristensen, H. S. (1983). 875 cases of bacterial meningitis: Diagnostic procedures and the impact of preadmission antibiotic therapy. part III of a three-part series. *J. Infect.* 7(3), 193–202.
- Borgström, E., Redin, D., Lundin, S., Berglund, E., Andersson, A. F. & Ahmadian, A. (2015). Phasing of single DNA molecules by massively parallel barcoding. *Nat. Commun.* 6, 7173.
- Bosch, A. A. T. M., van Houten, M. A., Bruin, J. P., Wijmenga-Monsuur, A. J., Trzciński, K., Bogaert, D., ... Sanders, E. A. M. (2016). Nasopharyngeal carriage of streptococcus pneumoniae and other bacteria in the 7th year after implementation of the pneumococcal conjugate vaccine in the netherlands. *Vaccine*, 34(4), 531–539.
- Botstein, D., White, R. L., Skolnick, M. & Davis, R. W. (1980). Construction of a genetic linkage map in man using restriction fragment length polymorphisms. *Am. J. Hum. Genet.* 32(3), 314–331.

- Brandtzaeg, P. (1993). Meningitis and septic shock as acute, fatal conditions. *Tidsskr. Nor. Laegeforen.* 113(16), 1994–1997.
- Breitling, R., Li, Y., Tesson, B. M., Fu, J., Wu, C., Wiltshire, T., . . . Jansen, R. C. (2008). Genetical genomics: Spotlight on QTL hotspots. *PLoS Genet.* 4(10), e1000232.
- Brittan, J. L., Buckeridge, T. J., Finn, A., Kadioglu, A. & Jenkinson, H. F. (2012). Pneumococcal neuraminidase a: An essential upper airway colonization factor for streptococcus pneumoniae. *Mol. Oral Microbiol.* 27(4), 270–283.
- Brogden, K. A. (2005). Antimicrobial peptides: Pore formers or metabolic inhibitors in bacteria? *Nat. Rev. Microbiol.* 3(3), 238–250.
- Brooks-Walter, A., Briles, D. E. & Hollingshead, S. K. (1999). The pspc gene of streptococcus pneumoniae encodes a polymorphic protein, PspC, which elicits cross-reactive antibodies to PspA and provides immunity to pneumococcal bacteremia. *Infect. Immun.* 67(12), 6533–6542.
- Brouwer, M. C., de Gans, J., Heckenberg, S. G. B., Zwinderman, A. H., van der Poll, T. & van de Beek, D. (2009). Host genetic susceptibility to pneumococcal and meningococcal disease: A systematic review and meta-analysis. *Lancet Infect. Dis.* 9(1), 31–44.
- Brouwer, M. C., Heckenberg, S. G. B., de Gans, J., Spanjaard, L., Reitsma, J. B. & van de Beek, D. (2010). Nationwide implementation of adjunctive dexamethasone therapy for pneumococcal meningitis. *Neurology*, 75(17), 1533–1539.
- Brouwer, M. C., McIntyre, P., Prasad, K., van de Beek, D., Mc, B. & D, V. D. B. (2013). Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst. Rev.* 6(6), CD004405.
- Brouwer, M. C., Tunkel, A. R. & van de Beek, D. (2010). Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. *Clin. Microbiol. Rev.* 23(3), 467–492.
- Brown, P. D., Davies, S. L., Speake, T. & Millar, I. D. (2004). Molecular mechanisms of cerebrospinal fluid production. *Neuroscience*, 129(4), 957–970.
- Bruchmann, S., Muthukumarasamy, U., Pohl, S., Preusse, M., Bielecka, A., Nicolai, T., . . . Häussler, S. (2015). Deep transcriptome profiling of clinical klebsiella pneumoniae isolates reveals strain and sequence type-specific adaptation. *Environ. Microbiol.* 17(11), 4690–4710.
- Brueggemann, A. B., Griffiths, D. T., Meats, E., Peto, T., Crook, D. W. & Spratt, B. G. (2003). Clonal relationships between invasive and carriage streptococcus pneumoniae and serotype- and clone-specific differences in invasive disease potential. *J. Infect. Dis.* 187(9), 1424–1432.
- Bryan, J. P., de Silva, H. R., Tavares, A., Rocha, H. & Scheld, W. M. (1990). Etiology and mortality of bacterial meningitis in northeastern brazil. *Rev. Infect. Dis.* 12(1), 128–135.

- Bryant, J. M., Grogono, D. M., Greaves, D., Foweraker, J., Roddick, I., Inns, T., ... Floto, R. A. (2013). Whole-genome sequencing to identify transmission of mycobacterium abscessus between patients with cystic fibrosis: A retrospective cohort study. *Lancet*, *381*(9877), 1551–1560.
- Brynildsrud, O., Bohlin, J., Scheffer, L. & Eldholm, V. (2016). Rapid scoring of genes in microbial pan-genome-wide association studies with scoary. *Genome Biol.* *17*(1), 238.
- Bucci, C., Lavitola, A., Salvatore, P., Del Giudice, L., Massardo, D. R., Bruni, C. B. & Alifano, P. (1999). Hypermutation in pathogenic bacteria. *Mol. Cell*, *3*(4), 435–445.
- Bulik-Sullivan, B. K., Loh, P.-R., Finucane, H. K., Ripke, S., Yang, J., Schizophrenia Working Group of the Psychiatric Genomics Consortium, ... Neale, B. M. (2015). LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* *47*(3), 291–295.
- Burgner, D., Jamieson, S. E. & Blackwell, J. M. (2006). Genetic susceptibility to infectious diseases: Big is beautiful, but will bigger be even better? *Lancet Infect. Dis.* *6*(10), 653–663.
- Burton, P. R., Clayton, D. G., Cardon, L. R., Craddock, N., Deloukas, P., Duncanson, A., ... Compston, A. (2007). Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*, *447*(7145), 661–678.
- Bush, W. S., Oetjens, M. T. & Crawford, D. C. (2016). Unravelling the human genome-phenome relationship using phenome-wide association studies. *Nat. Rev. Genet.* *17*(3), 129–145.
- Cartwright, R. a. (2005). DNA assembly with gaps (dawg): Simulating sequence evolution. *Bioinformatics*, *21*(SUPPL. 3), 31–38.
- Casanova, J.-L. (2015). Severe infectious diseases of childhood as monogenic inborn errors of immunity. *Proc. Natl. Acad. Sci. U. S. A.* *112*(51), E7128–37.
- Caugant, D. A., Hoiby, E. A., Magnus, P., Scheel, O., Hoel, T., Bjune, G., ... Froholm, L. O. (1994). Asymptomatic carriage of neisseria meningitidis in a randomly sampled population. *J. Clin. Microbiol.* *32*(2), 323–330.
- Cerutti, A. & Rescigno, M. (2008). The biology of intestinal immunoglobulin a responses. *Immunity*, *28*(6), 740–750.
- Chaguza, C., Andam, C. P., Harris, S. R., Cornick, J. E., Yang, M., Bricio-Moreno, L., ... Hanage, W. P. (2016). Recombination in streptococcus pneumoniae lineages increase with carriage duration and size of the polysaccharide capsule. *MBio*, *7*(5).
- Chang, C. C., Chow, C. C., Tellier, L. C., Vattikuti, S., Purcell, S. M. & Lee, J. J. (2015). Second-generation PLINK: Rising to the challenge of larger and richer datasets. *Gigascience*, *4*(1), 7.
- Chapman, S. J. & Hill, A. V. S. (2012). Human genetic susceptibility to infectious disease. *Nat. Rev. Genet.* *13*(3), 175–188.

- Chen, J. Q., Wu, Y., Yang, H., Bergelson, J., Kreitman, M. & Tian, D. (2009). Variation in the ratio of nucleotide substitution and indel rates across genomes in mammals and bacteria. *Mol. Biol. Evol.* 26(7), 1523–1531.
- Chen, P. E. & Shapiro, B. J. (2015). The advent of genome-wide association studies for bacteria. *Curr. Opin. Microbiol.* 25, 17–24.
- Cheng, L., Connor, T. R., Sirén, J., Aanensen, D. M. & Corander, J. (2013). Hierarchical and spatially explicit clustering of DNA sequences with BAPS software. *Mol. Biol. Evol.* 30(5), 1224–1228.
- Cheng, Q., Finkel, D. & Hostetter, M. K. (2000). Novel purification scheme and functions for a c3-binding protein from streptococcus pneumoniae. *Biochemistry*, 39(18), 5450–5457.
- Chengsong, Z. & Jianming, Y. (2009). Nonmetric multidimensional scaling corrects for population structure in association mapping with different sample types. *Genetics*, 182(3), 875–888.
- Chewapreecha, C., Harris, S. R., Croucher, N. J., Turner, C., Marttinen, P., Cheng, L., ... Bentley, S. D. (2014). Dense genomic sampling identifies highways of pneumococcal recombination. *Nat. Genet.* 46(3), 305–309.
- Chewapreecha, C., Marttinen, P., Croucher, N. J., Salter, S. J., Harris, S. R., Mather, A. E., ... Parkhill, J. (2014). Comprehensive identification of single nucleotide polymorphisms associated with beta-lactam resistance within pneumococcal mosaic genes. *PLoS Genet.* 10(8), e1004547.
- Choi, Y., Sims, G. E., Murphy, S., Miller, J. R. & Chan, A. P. (2012). Predicting the functional effect of amino acid substitutions and indels. *PLoS One*, 7(10), e46688.
- Christensen, H., Trotter, C. L., Hickman, M. & John Edmunds, W. (2014). Re-evaluating cost effectiveness of universal meningitis vaccination (bexsero) in england: Modelling study. *BMJ*, 349, g5725.
- Cingolani, P., Platts, A., Wang, L. L., Coon, M., Nguyen, T., Wang, L., ... Lu, X. (2012). A program for annotating and predicting the effects of single nucleotide polymorphisms, SnpEff: SNPs in the genome of drosophila melanogaster strain w1118 ; iso-2; iso-3. *Fly*, 6(2), 1–13.
- Cleary, D. W., Devine, V. T., Jefferies, J. M. C., Webb, J. S., Bentley, S. D., Gladstone, R. A., ... Clarke, S. C. (2016). Comparative genomics of carriage and disease isolates of *Streptococcus pneumoniae* serotype 22F reveals Lineage-Specific divergence and niche adaptation. *Genome Biol. Evol.* 8(4), 1243–1251.
- Cleverley, R. M., Barrett, J. R., Baslé, A., Bui, N. K., Hewitt, L., Solovyova, A., ... Lewis, R. J. (2014). Structure and function of a spectrin-like regulator of bacterial cytokinesis. *Nat. Commun.* 5, 5421.

- Cobey, S., Baskerville, E. B., Colijn, C., Hanage, W., Fraser, C. & Lipsitch, M. (2017). *Host population structure and treatment frequency maintain balancing selection on drug resistance.*
- Cobey, S. & Lipsitch, M. (2012). Niche and neutral effects of acquired immunity permit coexistence of pneumococcal serotypes. *Science*, 335(6074), 1376–1380.
- Cohen, C., Moyes, J., Tempia, S., Groom, M., Walaza, S., Pretorius, M., . . . Madhi, S. A. (2013). Severe influenza-associated respiratory infection in high HIV prevalence setting, south africa, 2009–2011. *Emerging Infectious Disease journal*, 19(11), 1766.
- Collins, C. & Didelot, X. (2017). *A phylogenetic method to perform Genome-Wide association studies in microbes that accounts for population structure and recombination.*
- Compeau, P. E. C., Pevzner, P. a. & Tesler, G. (2011). How to apply de bruijn graphs to genome assembly. *Nat. Biotechnol.* 29(11), 987–991.
- Cortes, A., Dendrou, C., Motyer, A., Jostins, L., Vukcevic, D., Dilthey, A., . . . McVean, G. (2017). *Bayesian analysis of genetic association across tree-structured routine healthcare data in the UK biobank.*
- Craig, A., Mai, J., Cai, S. & Jeyaseelan, S. (2009). Neutrophil recruitment to the lungs during bacterial pneumonia. *Infect. Immun.* 77(2), 568–575.
- Crain, M. J., Waltman, W. D., Turner, J. S., Yother, J., Talkington, D. F., McDaniel, L. S., . . . Briles, D. E. (1990). Pneumococcal surface protein a (PspA) is serologically highly variable and is expressed by all clinically important capsular serotypes of streptococcus pneumoniae. *Infect. Immun.* 58(10), 3293–3299.
- Cremers, A. J., Zomer, A. L., Gritzfeld, J. F., Ferwerda, G., van Hijum, S. A., Ferreira, D. M., . . . Hermans, P. W. (2014). The adult nasopharyngeal microbiome as a determinant of pneumococcal acquisition. *Microbiome*, 2(1), 44.
- Cron, L. E., Stol, K., Burghout, P., van Selm, S., Simonetti, E. R., Bootsma, H. J. & Hermans, P. W. M. (2011). Two DHH subfamily 1 proteins contribute to pneumococcal virulence and confer protection against pneumococcal disease. *Infect. Immun.* 79(9), 3697–3710.
- Croucher, N. J., Campo, J. J., Le, T. Q., Liang, X., Bentley, S. D., Hanage, W. P. & Lipsitch, M. (2017). Diverse evolutionary patterns of pneumococcal antigens identified by pangenome-wide immunological screening. *Proc. Natl. Acad. Sci. U. S. A.*
- Croucher, N. J., Coupland, P. G., Stevenson, A. E., Callendrello, A., Bentley, S. D. & Hanage, W. P. (2014). Diversification of bacterial genome content through distinct mechanisms over different timescales. *Nat. Commun.* 5, 5471.
- Croucher, N. J., Finkelstein, J. a., Pelton, S. I., Mitchell, P. K., Lee, G. M., Parkhill, J., . . . Lipsitch, M. (2013). Population genomics of post-vaccine changes in pneumococcal epidemiology. *Nat. Genet.* 45(6), 656–663.
- Croucher, N. J., Hanage, W. P., Harris, S. R., McGee, L., van der Linden, M., de Lencastre, H., . . . Bentley, S. D. (2014). Variable recombination dynamics during the

- emergence, transmission and 'disarming' of a multidrug-resistant pneumococcal clone. *BMC Biol.* 12(1), 49.
- Croucher, N. J., Harris, S. R., Barquist, L., Parkhill, J. & Bentley, S. D. (2012). A high-resolution view of genome-wide pneumococcal transformation. *PLoS Pathog.* 8(6).
- Croucher, N. J., Harris, S. R., Fraser, C., Quail, M. a., Burton, J., van der Linden, M., ... Bentley, S. D. (2011). Rapid pneumococcal evolution in response to clinical interventions. *Science*, 331(6016), 430–434.
- Croucher, N. J., Kagedan, L., Thompson, C. M., Parkhill, J., Bentley, S. D., Finkelstein, J. A., ... Hanage, W. P. (2015). Selective and genetic constraints on pneumococcal serotype switching. *PLoS Genet.* 11(3), 1–21.
- Croucher, N. J., Mitchell, A. M., Gould, K. a., Inverarity, D., Barquist, L., Feltwell, T., ... Bentley, S. D. (2013). Dominant role of nucleotide substitution in the diversification of serotype 3 pneumococci over decades and during a single infection. *PLoS Genet.* 9(10), e1003868.
- Croucher, N. J., Mostowy, R., Wymant, C., Turner, P., Bentley, S. D. & Fraser, C. (2016). Horizontal DNA transfer mechanisms of bacteria as weapons of intragenomic conflict. *PLoS Biol.* 14(3), e1002394.
- Croucher, N. J., Page, A. J., Connor, T. R., Delaney, A. J., Keane, J. A., Bentley, S. D., ... Harris, S. R. (2015). Rapid phylogenetic analysis of large samples of recombinant bacterial whole genome sequences using gubbins. *Nucleic Acids Res.* 43(3), e15–e15.
- Croucher, N. J., Vernikos, G. S., Parkhill, J. & Bentley, S. D. (2011). Identification, variation and transcription of pneumococcal repeat sequences. *BMC Genomics*, 12, 120.
- Croucher, N. J., Walker, D., Romero, P., Lennard, N., Paterson, G. K., Bason, N. C., ... Mitchell, T. J. (2009). Role of conjugative elements in the evolution of the multidrug-resistant pandemic clone streptococcus pneumoniaeSpain23F ST81. *J. Bacteriol.* 191(5), 1480–1489.
- Curtis, J., Luo, Y., Zenner, H. L., Cuchet-Lourenço, D., Wu, C., Lo, K., ... Nejentsev, S. (2015). Susceptibility to tuberculosis is associated with variants in the ASAP1 gene encoding a regulator of dendritic cell migration. *Nat. Genet.* 47(5), 523–527.
- Dagan, R., Givon-Lavi, N., Zamir, O., Sikuler-Cohen, M., Guy, L., Janco, J., ... Fraser, D. (2002). Reduction of nasopharyngeal carriage of streptococcus pneumoniae after administration of a 9-valent pneumococcal conjugate vaccine to toddlers attending day care centers. *J. Infect. Dis.* 185(7), 927–936.
- Dalquen, D. a., Anisimova, M., Gonnet, G. H. & Dessimoz, C. (2012). ALF—a simulation framework for genome evolution. *Mol. Biol. Evol.* 29(4), 1115–1123.
- Das, S. [Sayantan], Forer, L., Schönherr, S., Sidore, C., Locke, A. E., Kwong, A., ... Fuchsberger, C. (2016). Next-generation genotype imputation service and methods. *Nat. Genet.* 48(10), 1284–1287.

- Das, S. [Sudip], Lindemann, C., Young, B. C., Muller, J., Österreich, B., Ternet, N., ... Fraunholz, M. J. (2016). Natural mutations in a staphylococcus aureus virulence regulator attenuate cytotoxicity but permit bacteremia and abscess formation. *Proceedings of the National Academy of Sciences*, 113(22), E3101–E3110.
- Dave, S., Brooks-Walter, A., Pangburn, M. K. & McDaniel, L. S. (2001). PspC, a pneumococcal surface protein, binds human factor H. *Infect. Immun.* 69(5), 3435–3437.
- Davenport, E. E., Burnham, K. L., Radhakrishnan, J., Humburg, P., Hutton, P., Mills, T. C., ... Knight, J. C. (2016). Genomic landscape of the individual host response and outcomes in sepsis: A prospective cohort study. *Lancet Respir Med*, 4(4), 259–271.
- Davey Smith, G. & Hemani, G. (2014). Mendelian randomization: Genetic anchors for causal inference in epidemiological studies. *Hum. Mol. Genet.* 23(R1), R89–98.
- Davila, S., Wright, V. J., Khor, C. C., Sim, K. S., Binder, A., Breunis, W. B., ... Hibberd, M. L. (2010). Genome-wide association study identifies variants in the CFH region associated with host susceptibility to meningococcal disease. *Nat. Genet.* 42(9), 772–776.
- Dawid, S., Roche, A. M. & Weiser, J. N. (2007). The blp bacteriocins of streptococcus pneumoniae mediate intraspecies competition both in vitro and in vivo. *Infect. Immun.* 75(1), 443–451.
- De Chiara, M., Hood, D., Muzzi, A., Pickard, D. J., Perkins, T., Pizza, M., ... Donati, C. (2014). Genome sequencing of disease and carriage isolates of nontypeable haemophilus influenzae identifies discrete population structure. *Proc. Natl. Acad. Sci. U. S. A.* 111(14), 5439–5444.
- de Gans, J., van de Beek, D. & European Dexamethasone in Adulthood Bacterial Meningitis Study Investigators. (2002). Dexamethasone in adults with bacterial meningitis. *N. Engl. J. Med.* 347(20), 1549–1556.
- de Lange, K. M. & Barrett, J. C. (2015). Understanding inflammatory bowel disease via immunogenetics. *J. Autoimmun.*
- de Lange, K. M., Moutsianas, L., Lee, J. C., Lamb, C. A., Luo, Y., Kennedy, N. A., ... Barrett, J. C. (2017). Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. *Nat. Genet.* 49(2), 256–261.
- DeBardeleben, H. K., Lysenko, E. S., Dalia, A. B. & Weiser, J. N. (2014). Tolerance of a phage element by streptococcus pneumoniae leads to a fitness defect during colonization. *J. Bacteriol.* 196(14), 2670–2680.
- Deininger, S., Figueroa-Perez, I., Sigel, S., Stadelmaier, A., Schmidt, R. R., Hartung, T. & von Aulock, S. (2007). Use of synthetic derivatives to determine the minimal active structure of cytokine-inducing lipoteichoic acid. *Clin. Vaccine Immunol.* 14(12), 1629–1633.

- del Amo, E., Selva, L., de Sevilla, M. F., Ciruela, P., Brotons, P., Triviño, M., ... Muñoz-Almagro, C. (2015). Estimation of the invasive disease potential of streptococcus pneumoniae in children by the use of direct capsular typing in clinical specimens. *Eur. J. Clin. Microbiol. Infect. Dis.* 34(4), 705–711.
- Delaneau, O., Zagury, J.-F. & Marchini, J. (2013). Improved whole-chromosome phasing for disease and population genetic studies. *Nat. Methods*, 10(1), 5–6.
- Delany, I., Grifantini, R., Bartolini, E., Rappuoli, R. & Scarlato, V. (2006). Effect of neisseria meningitidis fur mutations on global control of gene transcription. *J. Bacteriol.* 188(7), 2483–2492.
- Denapaite, D., Brückner, R., Nuhn, M., Reichmann, P., Henrich, B., Maurer, P., ... Hakenbeck, R. (2010). The genome of streptococcus mitis B6 - what is a commensal? *PLoS One*, 5(2).
- Denny, J. C., Bastarache, L., Ritchie, M. D., Carroll, R. J., Zink, R., Mosley, J. D., ... Roden, D. M. (2013). Systematic comparison of phenome-wide association study of electronic medical record data and genome-wide association study data. *Nat. Biotechnol.* 31(12), 1102–1110.
- Desjardins, C. A., Cohen, K. A., Munsamy, V., Abeel, T., Maharaj, K., Walker, B. J., ... Pym, A. S. (2016). Genomic and functional analyses of mycobacterium tuberculosis strains implicate ald in d-cycloserine resistance. *Nat. Genet.* 48(5).
- Didelot, X., Walker, A. S., Peto, T. E., Crook, D. W. & Wilson, D. J. (2016). Within-host evolution of bacterial pathogens. *Nat. Rev. Microbiol.*
- Didelot, X. & Wilson, D. J. (2015). ClonalFrameML: Efficient inference of recombination in whole bacterial genomes. *PLoS Comput. Biol.* 11(2), e1004041.
- Dillard, J. P., Vandersea, M. W. & Yother, J. (1995). Characterization of the cassette containing genes for type 3 capsular polysaccharide biosynthesis in streptococcus pneumoniae. *J. Exp. Med.* 181(3), 973–983.
- Ding, L., Getz, G., Wheeler, D. A., Mardis, E. R., McLellan, M. D., Cibulskis, K., ... Wilson, R. K. (2008). Somatic mutations affect key pathways in lung adenocarcinoma. *Nature*, 455(7216), 1069–1075.
- Domenech, M., Garcia, E. & Moscoso, M. (2012). Biofilm formation in streptococcus pneumoniae. *Microb. Biotechnol.* 5(4), 455–465.
- Donati, C., Hiller, N. L., Tettelin, H., Muzzi, A., Croucher, N. J., Angiuoli, S. V., ... Massignani, V. (2010). Structure and dynamics of the pan-genome of streptococcus pneumoniae and closely related species. *Genome Biol.* 11(10), R107.
- Dubnau, D. (1999). DNA uptake in bacteria. *Annu. Rev. Microbiol.* 53(1), 217–244.
- Duplessis, M. & Moineau, S. (2001). Identification of a genetic determinant responsible for host specificity in streptococcus thermophilus bacteriophages. *Mol. Microbiol.* 41(2), 325–336.

- Durbin, R. (2014). Efficient haplotype matching and storage using the positional Burrows-Wheeler transform (PBWT). *Bioinformatics*, 30(9), 1266–1272.
- Earle, S. G., Wu, C.-H., Charlesworth, J., Stoesser, N., Gordon, N. C., Walker, T. M., ... Wilson, D. J. (2016). Identifying lineage effects when controlling for population structure improves power in bacterial association studies. *Nature Microbiology*, (April), 16041.
- Edgar, R. C. (2004). MUSCLE: Multiple sequence alignment with high accuracy and high throughput. *Nucleic Acids Res.* 32(5), 1792–1797.
- Efron, B., Hastie, T., Johnstone, I. & Tibshirani, R. (2004). Least angle regression. *Ann. Stat.* 32(2), 407–499.
- Ehrlich, G. D., Ahmed, A., Earl, J., Hiller, N. L., Costerton, J. W., Stoodley, P., ... Hu, F. Z. (2010). The distributed genome hypothesis as a rubric for understanding evolution in situ during chronic bacterial biofilm infectious processes. *FEMS Immunol. Med. Microbiol.* 59(3), 269–279.
- Eichler, E. E., Flint, J., Gibson, G., Kong, A., Leal, S. M., Moore, J. H. & Nadeau, J. H. (2010). Missing heritability and strategies for finding the underlying causes of complex disease. *Nat. Rev. Genet.* 11(6), 446–450.
- Enright, M. C. & Spratt, B. G. (1998). A multilocus sequence typing scheme for streptococcus pneumoniae: Identification of clones associated with serious invasive disease. *Microbiology*, 144(11), 3049–3060.
- Enright, M. C. & Spratt, B. G. (1999). Extensive variation in the *ddl* gene of penicillin-resistant streptococcus pneumoniae results from a hitchhiking effect driven by the penicillin-binding protein 2b gene. *Mol. Biol. Evol.* 16(12), 1687–1695.
- Evans, L., Tahmasbi, R., Vrieze, S., Abecasis, G., Das, S., Bjelland, D., ... Keller, M. (2017). *Comparison of methods that use whole genome data to estimate the heritability and genetic architecture of complex traits.*
- Eyre, D. W., Cule, M. L., Wilson, D. J., Griffiths, D., Vaughan, A., O'Connor, L., ... Walker, A. S. (2013). Diverse sources of *c. difficile* infection identified on Whole-Genome sequencing. *N. Engl. J. Med.* 369(13), 1195–1205.
- Fagarasan, S. & Honjo, T. (2003). Intestinal IgA synthesis: Regulation of front-line body defences. *Nat. Rev. Immunol.* 3(1), 63–72.
- Falush, D. & Bowden, R. (2006). Genome-wide association mapping in bacteria? *Trends Microbiol.* 14(8), 353–355.
- Farhat, M. R., Shapiro, B. J., Kieser, K. J., Sultana, R., Jacobson, K. R., Victor, T. C., ... Murray, M. (2013). Genomic analysis identifies targets of convergent positive selection in drug-resistant mycobacterium tuberculosis. *Nat. Genet.* 45(10), 1183–1189.

- Farhat, M. R., Shapiro, B., Sheppard, S. K., Colijn, C. & Murray, M. (2014). A phylogeny-based sampling strategy and power calculator informs genome-wide associations study design for microbial pathogens. *Genome Med.* 6(11), 101.
- Fellay, J., Shianna, K. V., Ge, D., Colombo, S., Ledergerber, B., Weale, M., ... Goldstein, D. B. (2007). A whole-genome association study of major determinants for host control of HIV-1. *Science*, 317(5840), 944–947.
- Felsenstein, J. (1985). Phylogenies and the comparative method. *Am. Nat.* 125(1), 1–15.
- Ferrándiz, M. J., Ardanuy, C., Liñares, J., Garcia-Arenzana, J. M., Cercenado, E., Fleites, A., ... Spanish Pneumococcal Infection Study Network. (2005). New mutations and horizontal transfer of rpoB among rifampin-resistant streptococcus pneumoniae from four spanish hospitals. *Antimicrob. Agents Chemother.* 49(6), 2237–2245.
- Ferreira, R. C., Pan-Hammarström, Q., Graham, R. R., Gateva, V., Fontán, G., Lee, A. T., ... Hammarström, L. (2010). Association of IFIH1 and other autoimmunity risk alleles with selective IgA deficiency. *Nat. Genet.* 42(9), 777–780.
- Fisher, R. A. (1919). XV.—The correlation between relatives on the supposition of mendelian inheritance. *Earth Environ. Sci. Trans. R. Soc. Edinb.* 52(2), 399–433.
- Ford, C. B., Shah, R. R., Maeda, M. K., Gagneux, S., Murray, M. B., Cohen, T., ... Fortune, S. M. (2013). Mycobacterium tuberculosis mutation rate estimates from different lineages predict substantial differences in the emergence of drug-resistant tuberculosis. *Nat. Genet.* 45(7), 784–790.
- Forney, G. D. (1973). The viterbi algorithm. *Proc. IEEE*, 61(3), 268–278.
- Franke, A., McGovern, D. P. B., Barrett, J. C., Wang, K., Radford-Smith, G. L., Ahmad, T., ... Parkes, M. (2010). Genome-wide meta-analysis increases to 71 the number of confirmed crohn’s disease susceptibility loci. *Nat. Genet.* 42(12), 1118–1125.
- Franke, L. & Jansen, R. C. (2009). eQTL analysis in humans. *Methods Mol. Biol.* 573, 311–328.
- Fransen, F., Heckenberg, S. G. B., Hamstra, H. J., Feller, M., Boog, C. J. P., van Putten, J. P. M., ... van der Ley, P. (2009). Naturally occurring lipid a mutants in neisseria meningitidis from patients with invasive meningococcal disease are associated with reduced coagulopathy. *PLoS Pathog.* 5(4), e1000396.
- Fraser, C., Lythgoe, K., Leventhal, G. E., Shirreff, G., Hollingsworth, T. D., Alizon, S. & Bonhoeffer, S. (2014). Virulence and pathogenesis of HIV-1 infection: An evolutionary perspective. *Science*, 343(6177), 1243727.
- Friedman, J., Hastie, T. & Tibshirani, R. (2010). Regularization paths for generalized linear models via coordinate descent. *J. Stat. Softw.* 33(1), 1–22.
- Fuchsberger, C., Flannick, J., Teslovich, T. M., Mahajan, A., Agarwala, V., Gaulton, K. J., ... McCarthy, M. I. (2016). The genetic architecture of type 2 diabetes. *Nature*, 536(7614), 41–47.

- Fusi, N., Lippert, C., Lawrence, N. D. & Stegle, O. (2014). Warped linear mixed models for the genetic analysis of transformed phenotypes. *Nat. Commun.* 5(May), 4890.
- Gang, T. B., Hanley, G. A. & Agrawal, A. (2015). C-reactive protein protects mice against pneumococcal infection via both phosphocholine-dependent and phosphocholine-independent mechanisms. *Infect. Immun.* 83(5), 1845–1852.
- Ganna, A., Genovese, G., Howrigan, D. P., Byrnes, A., Kurki, M. I., Zekavat, S. M., ... Neale, B. M. (2016). Ultra-rare disruptive and damaging mutations influence educational attainment in the general population. *Nat. Neurosci.* 19(12), 1563–1565.
- Gardner, S. N. & Hall, B. G. (2013). When whole-genome alignments just won't work: kSNP v2 software for alignment-free SNP discovery and phylogenetics of hundreds of microbial genomes. *PLoS One*, 8(12), e81760.
- Garland & Ives, A. R. (2000). Using the past to predict the present: Confidence intervals for regression equations in phylogenetic comparative methods. *Am. Nat.* 155(3), 346–364.
- Garrison, E. & Marth, G. (2012). Haplotype-based variant detection from short-read sequencing. arXiv: 1207.3907 [q-bio.GN]
- Gascuel, O. (1997). BIONJ: An improved version of the NJ algorithm based on a simple model of sequence data. *Mol. Biol. Evol.* 14(7), 685–695.
- Ge, T., Chen, C.-Y., Neale, B. M., Sabuncu, M. R. & Smoller, J. W. (2017). Phenome-wide heritability analysis of the UK biobank. *PLoS Genet.* 13(4), e1006711.
- Gerlini, A., Colomba, L., Furi, L., Braccini, T., Manso, A. S., Pammolli, A., ... Oggioni, M. R. (2014). The role of host and microbial factors in the pathogenesis of pneumococcal bacteraemia arising from a single bacterial cell bottleneck. *PLoS Pathog.* 10(3).
- Gillberg, J., Marttinen, P., Pirinen, M., Kangas, A. J., Soininen, P., Ali, M., ... Kaski, S. (2016). Multiple output regression with latent noise. *J. Mach. Learn. Res.* 17(122), 1–35.
- Ginsberg, L. (2004). Difficult and recurrent meningitis. *J. Neurol. Neurosurg. Psychiatry*, 75(suppl 1), i16–i21.
- Glover, D. T., Hollingshead, S. K. & Briles, D. E. (2008). Streptococcus pneumoniae surface protein PcpA elicits protection against lung infection and fatal sepsis. *Infect. Immun.* 76(6), 2767–2776.
- Gog, S., Beller, T., Moffat, A. & Petri, M. (2014). From theory to practice: Plug and play with succinct data structures. In J. Gudmundsson & J. Katajainen (Eds.), *Experimental algorithms SE - 28* (Vol. 8504, pp. 326–337). Lecture Notes in Computer Science. Springer International Publishing.
- Gouy, M., Guindon, S. & Gascuel, O. (2010). SeaView version 4: A multiplatform graphical user interface for sequence alignment and phylogenetic tree building. *Mol. Biol. Evol.* 27(2), 221–224.

- Gregory, S. G., Barlow, K. F., McLay, K. E., Kaul, R., Swarbreck, D., Dunham, A., ... Prigmore, E. (2006). The DNA sequence and biological annotation of human chromosome 1. *Nature*, *441*(7091), 315–321.
- Griffiths, N. J., Hill, D. J., Borodina, E., Sessions, R. B., Devos, N. I., Feron, C. M., ... Virji, M. (2011). Meningococcal surface fibril (msf) binds to activated vitronectin and inhibits the terminal complement pathway to increase serum resistance. *Mol. Microbiol.* *82*(5), 1129–1149.
- Gripenland, J., Netterling, S., Loh, E., Tiensuu, T., Toledo-Arana, A. & Johansson, J. (2010). RNAs: Regulators of bacterial virulence. *Nat. Rev. Microbiol.* *8*(12), 857–866.
- Gritzfeld, J. F., Cremers, A. J. H., Ferwerda, G., Ferreira, D. M., Kadioglu, A., Hermans, P. W. M. & Gordon, S. B. (2014). Density and duration of experimental human pneumococcal carriage. *Clin. Microbiol. Infect.* *20*(12), O1145–51.
- Gurevich, A., Saveliev, V., Vyahhi, N. & Tesler, G. (2013). QUASt: Quality assessment tool for genome assemblies. *Bioinformatics*, *29*(8), 1072–1075.
- Gusella, J. F., Wexler, N. S., Conneally, P. M., Naylor, S. L., Anderson, M. A., Tanzi, R. E., ... Sakaguchi, A. Y. (1983). A polymorphic DNA marker genetically linked to huntington's disease. *Nature*, *306*(5940), 234–238.
- Habets, M. G. J. L., Rozen, D. E. & Brockhurst, M. a. (2012). Variation in streptococcus pneumoniae susceptibility to human antimicrobial peptides may mediate intraspecific competition. *Proceedings of the Royal Society B: Biological Sciences*, *279*(1743), 3803–3811.
- Hammit, L. L., Bruden, D. L., Butler, J. C., Baggett, H. C., Hurlburt, D. A., Reasonover, A. & Hennessy, T. W. (2006). Indirect effect of conjugate vaccine on adult carriage of streptococcus pneumoniae: An explanation of trends in invasive pneumococcal disease. *J. Infect. Dis.* *193*(11), 1487–1494.
- Hanage, W. P., Fraser, C., Tang, J., Connor, T. R. & Corander, J. (2009). Hyper-recombination, diversity, and antibiotic resistance in pneumococcus. *Science*, *324*(5933), 1454–1457.
- Hanage, W. P., Kaijalainen, T., Herva, E., Saukkoriipi, A., Syrjänen, R. & Spratt, B. G. (2005). Using multilocus sequence data to define the pneumococcus. *J. Bacteriol.* *187*(17), 6223–6230.
- Hardin, G. (1960). The competitive exclusion principle. *Science*, *131*(3409), 1292–1297.
- Harpaz, R., Dahl, R. & Dooling, K. (2016). The prevalence of immunocompromised adults: United states, 2013. *Open Forum Infect Dis*, *3*(suppl_1).
- Harvey, R. M., Ogunniyi, A. D., Chen, A. Y. & Paton, J. C. (2011). Pneumolysin with low hemolytic activity confers an early growth advantage to streptococcus pneumoniae in the blood. *Infect. Immun.* *79*(10), 4122–4130.

- Hasbun, R., Abrahams, J., Jekel, J. & Quagliarello, V. J. (2001). Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N. Engl. J. Med.* 345(24), 1727–1733.
- Hathaway, L. J., Brugger, S. D., Morand, B., Bangert, M., Rotzetter, J. U., Hauser, C., ... Mühlemann, K. (2012). Capsule type of streptococcus pneumoniae determines growth phenotype. *PLoS Pathog.* 8(3), e1002574.
- Haubold, B., Klötzl, F. & Pfaffelhuber, P. (2015). Andi: Fast and accurate estimation of evolutionary distances between closely related genomes. *Bioinformatics*, 31(8), 1169–1175.
- Hausdorff, W. P., Bryant, J., Paradiso, P. R. & Siber, G. R. (2000). Which pneumococcal serogroups cause the most invasive disease: Implications for conjugate vaccine formulation and use, part I. *Clin. Infect. Dis.* 30(1), 100–121.
- Hava, D. L. & Camilli, A. (2002). Large-scale identification of serotype 4 streptococcus pneumoniae virulence factors. *Mol. Microbiol.* 45(5), 1389–1406.
- Hebiri, M. & Lederer, J. C. (2012). How correlations influence lasso prediction. arXiv: 1204.1605 [math.ST]
- Heckenberg, S. G. B., Brouwer, M. C., van der Ende, A. & van de Beek, D. (2012). Adjuvantic dexamethasone in adults with meningococcal meningitis. *Neurology*, 79(15), 1563–1569.
- Heinze, G. & Ploner, M. (2003). Fixing the nonconvergence bug in logistic regression with SPLUS and SAS. *Comput. Methods Programs Biomed.* 71(2), 181–187.
- Herbert, A. P., Makou, E., Chen, Z. A., Kerr, H., Richards, A., Rappsilber, J. & Barlow, P. N. (2015). Complement evasion mediated by enhancement of captured factor h: Implications for protection of Self-Surfaces from complement. *J. Immunol.* 195(10), 4986–4998.
- Hill, A. (2012). Evolution, revolution and heresy in the genetics of infectious disease susceptibility. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 367(1590), 840–849.
- Hill, P. C., Townend, J., Antonio, M., Akisanya, B., Ebruke, C., Lahai, G., ... Adegbola, R. A. (2010). Transmission of streptococcus pneumoniae in rural gambian villages: A longitudinal study. *Clin. Infect. Dis.* 50(11), 1468–1476.
- Hiller, N. L., Janto, B., Hogg, J. S., Boissy, R., Yu, S., Powell, E., ... Hu, F. Z. (2007). Comparative genomic analyses of seventeen streptococcus pneumoniae strains: Insights into the pneumococcal supragenome. *J. Bacteriol.* 189(22), 8186–8195.
- Hirschhorn, J. N. & Daly, M. J. (2005). Genome-wide association studies for common diseases and complex traits. *Nat. Rev. Genet.* 6(2), 95–108.
- Hirst, R. A., Kadioglu, A., O’Callaghan, C. & Andrew, P. W. (2004). The role of pneumolysin in pneumococcal pneumonia and meningitis. *Clin. Exp. Immunol.* 138(2), 195–201.

- Högberg, L., Geli, P., Ringberg, H., Melander, E., Lipsitch, M. & Ekdahl, K. (2007). Age- and serogroup-related differences in observed durations of nasopharyngeal carriage of penicillin-resistant pneumococci. *J. Clin. Microbiol.* 45(3), 948–952.
- Hollingshead, S. K., Becker, R. & Briles, D. E. (2000). Diversity of PspA: Mosaic genes and evidence for past recombination in streptococcus pneumoniae. *Infect. Immun.* 68(10), 5889–5900.
- Holt, K. E., Wertheim, H., Zadoks, R. N., Baker, S., Whitehouse, C. A., Dance, D., ... Thomson, N. R. (2015). Genomic analysis of diversity, population structure, virulence, and antimicrobial resistance in klebsiella pneumoniae, an urgent threat to public health. *Proc. Natl. Acad. Sci. U. S. A.* 112(27), E3574–81.
- Hoskins, J., Alborn, W. E., Arnold, J., Blaszczyk, L. C., Burgett, S., DeHoff, B. S., ... States, U. (2001). Genome of the bacterium streptococcus pneumoniae strain R6. *J. Bacteriol.* 183(19), 5709–5717.
- Hosmer, D. W., Jr., Lemeshow, S. & Sturdivant, R. X. (2013). *Applied logistic regression*. John Wiley & Sons.
- Howden, B. P., Gladman, S. L., Stinear, T. P., Tobias, N. J., Monk, I. R., Seemann, T. & Gao, W. (2015). Large tandem chromosome expansions facilitate niche adaptation during persistent infection with drug-resistant staphylococcus aureus. *Microbial Genomics*, 1(1), 1–13.
- Howie, B. N., Donnelly, P. & Marchini, J. (2009). A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. *PLoS Genet.* 5(6), e1000529.
- Howie, B., Marchini, J. & Stephens, M. (2011). Genotype imputation with thousands of genomes. *G3*, 1(6), 457–470.
- Hu, X., Yuan, J., Shi, Y., Lu, J., Liu, B., Li, Z., ... Fan, W. (2012). pIRS: Profile-based illumina pair-end reads simulator. *Bioinformatics*, 28(11), 1533–1535.
- Hung, M.-C. & Christodoulides, M. (2013). The biology of neisseria adhesins. *Biology*, 2(3), 1054–1109.
- Hunt, M., Mather, A. E., Sánchez-Busó, L., Page, A. J., Parkhill, J., Keane, J. A. & Harris, S. R. (2017). *ARIBA: Rapid antimicrobial resistance genotyping directly from sequencing reads*.
- Hyams, C., Camberlein, E., Cohen, J. M., Bax, K. & Brown, J. S. (2010). The streptococcus pneumoniae capsule inhibits complement activity and neutrophil phagocytosis by multiple mechanisms. *Infect. Immun.* 78(2), 704–715.
- Hyams, C., Trzcinski, K., Camberlein, E., Weinberger, D. M., Chimalapati, S., Noursadeghi, M., ... Brown, J. S. (2013). Streptococcus pneumoniae capsular serotype invasiveness correlates with the degree of factor H binding and opsonization with C3b/iC3b. *Infect. Immun.* 81(1), 354–363.

- Iannelli, F., Oggioni, M. R. & Pozzi, G. (2002). Allelic variation in the highly polymorphic locus *pspc* of streptococcus pneumoniae. *Gene*, 284(1-2), 63–71.
- Imöhl, M., Reinert, R. R., Ocklenburg, C. & van der Linden, M. (2010). Association of serotypes of streptococcus pneumoniae with age in invasive pneumococcal disease. *J. Clin. Microbiol.* 48(4), 1291–1296.
- Inouye, M., Dashnow, H., Raven, L.-A., Schultz, M. B., Pope, B. J., Tomita, T., . . . Holt, K. E. (2014). SRST2: Rapid genomic surveillance for public health and hospital microbiology labs. *Genome Med.* 6(11), 90.
- International HapMap Consortium. (2005). A haplotype map of the human genome. *Nature*, 437(7063), 1299–1320.
- International HapMap Consortium, Frazer, K. A., Ballinger, D. G., Cox, D. R., Hinds, D. A., Stuve, L. L., . . . Stewart, J. (2007). A second generation human haplotype map of over 3.1 million SNPs. *Nature*, 449(7164), 851–861.
- International Schizophrenia Consortium, Purcell, S. M., Wray, N. R., Stone, J. L., Visser, P. M., O’Donovan, M. C., . . . Sklar, P. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*, 460(7256), 748–752.
- Iovino, F., Engelen-Lee, J.-Y., Brouwer, M., van de Beek, D., van der Ende, A., Valls Seron, M., . . . Henriques-Normark, B. (2017). pIgR and PECAM-1 bind to pneumococcal adhesins RrgA and PspC mediating bacterial brain invasion. *J. Exp. Med.*
- Iqbal, Z., Caccamo, M., Turner, I., Flicek, P. & McVean, G. (2012). De novo assembly and genotyping of variants using colored de bruijn graphs. *Nat. Genet.* 44(2), 226–232.
- Jackson, C. H. (2011). Multi-State models for panel data: The msm package for R. *J. Stat. Softw.* 38(8), 1–28.
- Jafri, R. Z., Ali, A., Messonnier, N. E., Tevi-Benissan, C., Durrheim, D., Eskola, J., . . . Abramson, J. (2013). Global epidemiology of invasive meningococcal disease. *Popul. Health Metr.* 11(1), 17.
- Jaillard, M., Tournoud, M., Lima, L., Lacroix, V., Veyrieras, J.-B. & Jacob, L. (2017). *Representing genetic determinants in bacterial GWAS with compacted de bruijn graphs.*
- Jallow, M., Teo, Y. Y., Small, K. S., Rockett, K. A., Deloukas, P., Clark, T. G., . . . Malaria Genomic Epidemiology Network. (2009). Genome-wide and fine-resolution association analysis of malaria in west africa. *Nat. Genet.* 41(6), 657–665.
- Janoff, E. N., Fasching, C., Orenstein, J. M., Rubins, J. B., Opstad, N. L. & Dalmasso, A. P. (1999). Killing of streptococcus pneumoniae by capsular polysaccharide-specific polymeric IgA, complement, and phagocytes. *J. Clin. Invest.* 104(8), 1139–1147.
- Janulczyk, R., Iannelli, F., Sjöholm, A. G., Pozzi, G. & Björck, L. (2000). Hic, a novel surface protein of streptococcus pneumoniae that interferes with complement function. *J. Biol. Chem.* 275(47), 37257–37263.

- Jedrzejewski, M. J., Lamani, E. & Becker, R. S. (2001). Characterization of selected strains of pneumococcal surface protein a. *J. Biol. Chem.* 276(35), 33121–33128.
- Jennett, B. & Bond, M. (1975). Assessment of outcome after severe brain damage: A practical scale. *Lancet*, 305(7905), 480–484.
- Jepson, A. (1998). Twin studies for the analysis of heritability of infectious diseases. *Bull. Inst. Pasteur*, 96(2), 71–81.
- Johansson, J., Mandin, P., Renzoni, A., Chiaruttini, C., Springer, M. & Cossart, P. (2002). An RNA thermosensor controls expression of virulence genes in listeria monocytogenes. *Cell*, 110(5), 551–561.
- Jolley, K. A. & Maiden, M. (2010). BIGSdb: Scalable analysis of bacterial genome variation at the population level. *BMC Bioinformatics*, 11, 595.
- Jombart, T., Devillard, S. & Balloux, F. (2010). Discriminant analysis of principal components: A new method for the analysis of genetically structured populations. *BMC Genet.* 11(1), 94.
- Jones, M. R., Simms, B. T., Lupa, M. M., Kogan, M. S. & Mizgerd, J. P. (2005). Lung NF-kappaB activation and neutrophil recruitment require IL-1 and TNF receptor signaling during pneumococcal pneumonia. *J. Immunol.* 175(11), 7530–7535.
- Jorth, P., Staudinger, B. J., Wu, X., Hisert, K. B., Hayden, H., Garudathri, J., ... Singh, P. K. (2015). Regional isolation drives bacterial diversification within cystic fibrosis lungs. *Cell Host Microbe*, 18(3), 307–319.
- Kadie, C. M. & Heckerman, D. (2017). *Ludicrous speed linear mixed models for Genome-Wide association studies.*
- Kadioglu, A., Taylor, S., Iannelli, F., Pozzi, G., Mitchell, T. J. & Andrew, P. W. (2002). Upper and lower respiratory tract infection by streptococcus pneumoniae is affected by pneumolysin deficiency and differences in capsule type. *Infect. Immun.* 70(6), 2886–2890.
- Kadioglu, A., Weiser, J. N., Paton, J. C. & Andrew, P. W. (2008). The role of streptococcus pneumoniae virulence factors in host respiratory colonization and disease. *Nat. Rev. Microbiol.* 6(4), 288–301.
- Kapatai, G., Sheppard, C. L., Troxler, L. J., Litt, D. J., Furrer, J., Hilty, M. & Fry, N. K. (2017). Pneumococcal 23B molecular subtype identified using whole genome sequencing. *Genome Biol. Evol.*
- Kelley, D. R., Schatz, M. C. & Salzberg, S. L. (2010). Quake: Quality-aware detection and correction of sequencing errors. *Genome Biol.* 11(11), R116.
- Kendall, M. & Colijn, C. (2015). A tree metric using structure and length to capture distinct phylogenetic signals.
- Kendall, M. & Colijn, C. (2016). Mapping phylogenetic trees to reveal distinct patterns of evolution. *Mol. Biol. Evol.* (1200), 1–5.

- Kennemann, L., Didelot, X., Aebischer, T., Kuhn, S., Drescher, B., Droege, M., ... Suerbaum, S. (2011). *Helicobacter pylori* genome evolution during human infection. *Proceedings of the National Academy of Sciences*, *108*(12), 5033–5038.
- Kent, W. J. (2002). BLAT—The BLAST-Like alignment tool. *Genome Res.* *12*(4), 656–664.
- Kett, K., Brandtzaeg, P., Radl, J. & Haaijman, J. J. (1986). Different subclass distribution of IgA-producing cells in human lymphoid organs and various secretory tissues. *J. Immunol.* *136*(10), 3631–3635.
- Khan, M. N. & Pichichero, M. E. (2012). Vaccine candidates PhtD and PhtE of streptococcus pneumoniae are adhesins that elicit functional antibodies in humans. *Vaccine*, *30*(18), 2900–2907.
- Khatib, U., van de Beek, D., Lees, J. A. & Brouwer, M. C. (2016). Adults with suspected central nervous system infection: A prospective study of diagnostic accuracy. *J. Infect.*
- Khor, C. C., Chapman, S. J., Vannberg, F. O., Dunne, A., Murphy, C., Ling, E. Y., ... Hill, A. V. S. (2007). A mal functional variant is associated with protection against invasive pneumococcal disease, bacteremia, malaria and tuberculosis. *Nat. Genet.* *39*(4), 523–528.
- Khor, C. C., Chau, T. N. B., Pang, J., Davila, S., Long, H. T., Ong, R. T. H., ... Simmons, C. P. (2011). Genome-wide association study identifies susceptibility loci for dengue shock syndrome at MICB and PLCE1. *Nat. Genet.* *43*(11), 1139–1141.
- King, D. E. (2009). Dlib-ml : A machine learning toolkit. *J. Mach. Learn. Res.* *10*, 1755–1758.
- King, S. J., Hippe, K. R., Gould, J. M., Bae, D., Peterson, S., Cline, R. T., ... Weiser, J. N. (2004). Phase variable desialylation of host proteins that bind to streptococcus pneumoniae in vivo and protect the airway. *Mol. Microbiol.* *54*(1), 159–171.
- Kircher, M., Witten, D. M., Jain, P., O’Roak, B. J., Cooper, G. M. & Shendure, J. (2014). A general framework for estimating the relative pathogenicity of human genetic variants. *Nat. Genet.* *46*(3), 310–315.
- Kjos, M., Miller, E., Slager, J., Lake, F. B., Gericke, O., Roberts, I. S., ... Veening, J.-W. (2016). Expression of streptococcus pneumoniae bacteriocins is induced by antibiotics via regulatory interplay with the competence system. *PLoS Pathog.* *12*(2), e1005422.
- Klambauer, G., Schwarzbauer, K., Mayr, A., Clevert, D.-A., Mitterecker, A., Bodenhofer, U. & Hochreiter, S. (2012). cn.MOPS: Mixture of poisson for discovering copy number variations in next-generation sequencing data with a low false discovery rate. *Nucleic Acids Res.* *40*(9), e69.
- Kleckner, N. (1981). Transposable elements in prokaryotes. *Annu. Rev. Genet.* *15*(1), 341–404.

- Klein, R. J., Zeiss, C., Chew, E. Y., Tsai, J.-Y., Sackler, R. S., Haynes, C., ... Hoh, J. (2005). Complement factor H polymorphism in age-related macular degeneration. *Science*, 308(5720), 385–389.
- Klugman, K. P. (2001). Efficacy of pneumococcal conjugate vaccines and their effect on carriage and antimicrobial resistance. *Lancet Infect. Dis.* 1(2), 85–91.
- Knol, M. J., Wagenvoort, G. H. J., Sanders, E. A. M., Elberse, K., Vlamincx, B. J., Melker, H. E. d. & Ende, A. v. d. (2015). Invasive pneumococcal disease 3 years after introduction of 10-valent pneumococcal conjugate vaccine, the netherlands. *Emerging Infectious Disease journal*, 21(11), 2040.
- Knoll, M. D., Moisi, J. C., Muhib, F. B., Wonodi, C. B., Lee, E. H., Grant, L., ... PneumoADIP-Sponsored Surveillance Investigators. (2009). Standardizing surveillance of pneumococcal disease. *Clin. Infect. Dis.* 48 Suppl 2, S37–48.
- Ko, D. C. & Urban, T. J. (2013). Understanding human variation in infectious disease susceptibility through clinical and cellular GWAS. *PLoS Pathog.* 9(8), e1003424.
- Kolaczkowska, E. & Kubes, P. (2013). Neutrophil recruitment and function in health and inflammation. *Nat. Rev. Immunol.* 13(3), 159–175.
- Kono, M., Zafar, M. A., Zuniga, M., Roche, A. M., Hamaguchi, S. & Weiser, J. N. (2016). Single cell bottlenecks in the pathogenesis of streptococcus pneumoniae. *PLoS Pathog.* 12(10), e1005887.
- Koopmans, M. M., Bijlsma, M. W., Brouwer, M. C., van de Beek, D. & van der Ende, A. (2017). *Listeria monocytogenes* meningitis in the netherlands, 1985-2014: A nationwide surveillance study. *J. Infect.* 75(1), 12–19.
- Koppe, U., Suttorp, N. & Opitz, B. (2012). Recognition of streptococcus pneumoniae by the innate immune system. *Cell. Microbiol.* 14(4), 460–466.
- Kosiol, C., Holmes, I. & Goldman, N. (2007). An empirical codon model for protein sequence evolution. *Mol. Biol. Evol.* 24(7), 1464–1479.
- Kovács, M., Halfmann, A., Fedtke, I., Heintz, M., Peschel, A., Vollmer, W., ... Brückner, R. (2006). A functional *dlt* operon, encoding proteins required for incorporation of d-alanine in teichoic acids in gram-positive bacteria, confers resistance to cationic antimicrobial peptides in streptococcus pneumoniae. *J. Bacteriol.* 188(16), 5797–5805.
- Kremer, P. H. C., Lees, J. A., Koopmans, M. M., Ferwerda, B., Arends, A. W. M., Feller, M. M., ... Bentley, S. D. (2017). Benzalkonium tolerance genes and outcome in *listeria monocytogenes* meningitis. *Clin. Microbiol. Infect.* 23(4), 265.e1–265.e7.
- Kruger, P., Saffarzadeh, M., Weber, A. N. R., Rieber, N., Radsak, M., von Bernuth, H., ... Hartl, D. (2015). Neutrophils: Between host defence, immune modulation, and tissue injury. *PLoS Pathog.* 11(3), e1004651.
- Kuipers, K., Gallay, C., Martinek, V., Rohde, M., Martinková, M., van der Beek, S. L., ... de Jonge, M. I. (2016). Highly conserved nucleotide phosphatase essential for

- membrane lipid homeostasis in streptococcus pneumoniae. *Mol. Microbiol.* 101(1), 12–26.
- Kulohoma, B. W., Cornick, J. E., Chaguz, C., Yalcin, F., Harris, S. R., Gray, K. J., ... Heyderman, R. S. (2015). Comparative genomic analysis of meningitis and bacteremia causing pneumococci identifies a common core genome. *Infect. Immun.* (August), IAI.00814–15.
- La Scolea, L. J. & Dryja, D. (1984). Quantitation of bacteria in cerebrospinal fluid and blood of children with meningitis and its diagnostic significance. *J. Clin. Microbiol.* 19(2), 187–190.
- Laabei, M., Recker, M., Rudkin, J. K., Aldeljawi, M., Gulay, Z., Sloan, T. J., ... Massey, R. C. (2014). Predicting the virulence of MRSA from its genome sequence. *Genome Res.* 24(5), 839–849.
- Lambris, J. D., Ricklin, D. & Geisbrecht, B. V. (2008). Complement evasion by human pathogens. *Nat. Rev. Microbiol.* 6(2), 132–142.
- Lander, E. & Kruglyak, L. (1995). Genetic dissection of complex traits: Guidelines for interpreting and reporting linkage results. *Nat. Genet.* 11(3), 241–247.
- Lander, E., Linton, L. M., Birren, B., Nusbaum, C., Zody, M. C., Baldwin, J., ... International Human Genome Sequencing Consortium. (2001). Initial sequencing and analysis of the human genome. *Nature*, 409(6822), 860–921.
- Lanie, J. A., Ng, W.-L., Kazmierczak, K. M., Andrzejewski, T. M., Davidsen, T. M., Wayne, K. J., ... Winkler, M. E. (2007). Genome sequence of avery's virulent serotype 2 strain D39 of streptococcus pneumoniae and comparison with that of unencapsulated laboratory strain R6. *J. Bacteriol.* 189(1), 38–51.
- Lee, C. J., Banks, S. D. & Li, J. P. (1991). Virulence, immunity, and vaccine related to streptococcus pneumoniae. *Crit. Rev. Microbiol.* 18(2), 89–114.
- Lee, S. H., Wray, N. R., Goddard, M. E. & Visscher, P. M. (2011). Estimating missing heritability for disease from genome-wide association studies. *Am. J. Hum. Genet.* 88(3), 294–305.
- Lee, S., Abecasis, G. R., Boehnke, M. & Lin, X. (2014). Rare-variant association analysis: Study designs and statistical tests. *Am. J. Hum. Genet.* 95(1), 5–23.
- Lee, S., Emond, M. J., Bamshad, M. J., Barnes, K. C., Rieder, M. J., Nickerson, D. a., ... Lin, X. (2012). Optimal unified approach for rare-variant association testing with application to small-sample case-control whole-exome sequencing studies. *Am. J. Hum. Genet.* 91, 224–237.
- Lefébure, T. & Stanhope, M. J. (2007). Evolution of the core and pan-genome of streptococcus: Positive selection, recombination, and genome composition. *Genome Biol.* 8(5), R71.

- Lehtinen, S., Blanquart, F., Croucher, N. J., Turner, P., Lipsitch, M. & Fraser, C. (2017). Evolution of antibiotic resistance is linked to any genetic mechanism affecting bacterial duration of carriage. *Proc. Natl. Acad. Sci. U. S. A.* 114(5), 1075–1080.
- Levandowsky, M. & Winter, D. (1971). Distance between sets. *Nature*, 234(5323), 34–35.
- Levin, H. L. & Moran, J. V. (2011). Dynamic interactions between transposable elements and their hosts. *Nat. Rev. Genet.* 12(9), 615–627.
- Levine, O. S., Cherian, T., Hajjeh, R. & Deloria Knoll, M. (2009). Progress and future challenges in coordinated surveillance and detection of pneumococcal and hib disease in developing countries. *Clin. Infect. Dis.* 48(Supplement_2), S33–S36.
- Li, B. & Leal, S. M. (2008). Methods for detecting associations with rare variants for common diseases: Application to analysis of sequence data. *Am. J. Hum. Genet.* 83(3), 311–321.
- Li, H. (2011). A statistical framework for SNP calling, mutation discovery, association mapping and population genetical parameter estimation from sequencing data. *Bioinformatics*, 27(21), 2987–2993.
- Li, H. (2013). Aligning sequence reads, clone sequences and assembly contigs with BWA-MEM, 3.
- Li, J., Li, J.-W., Feng, Z., Wang, J., An, H., Liu, Y., ... Zhang, J.-R. (2016). Epigenetic switch driven by DNA inversions dictates phase variation in streptococcus pneumoniae. *PLoS Pathog.* 12(7), e1005762.
- Li, R., Li, Y., Zheng, H., Luo, R., Zhu, H., Li, Q., ... Wang, J. (2010). Building the sequence map of the human pan-genome. *Nat. Biotechnol.* 28(1), 57–63.
- Li, Y., Thompson, C. M., Trzciński, K. & Lipsitch, M. (2013). Within-host selection is limited by an effective population of streptococcus pneumoniae during nasopharyngeal colonization. *Infect. Immun.* 81(12), 4534–4543.
- Li, Y., Weinberger, D. M., Thompson, C. M., Trzciński, K. & Lipsitch, M. (2013). Surface charge of streptococcus pneumoniae predicts serotype distribution. *Infect. Immun.* 81(12), 4519–4524.
- Liley, J., Todd, J. A. & Wallace, C. (2017). A method for identifying genetic heterogeneity within phenotypically defined disease subgroups. *Nat. Genet.* 49(2), 310–316.
- Lippert, C., Listgarten, J., Liu, Y., Kadie, C. M., Davidson, R. I. & Heckerman, D. (2011). FaST linear mixed models for genome-wide association studies. *Nat. Methods*, 8(10), 833–835.
- Lipsitch, M. (2001). Measuring and interpreting associations between antibiotic use and penicillin resistance in streptococcus pneumoniae. *Clin. Infect. Dis.* 32, 1044–1054.
- Lipsitch, M., Abdullahi, O., D'Amour, A., Xie, W., Weinberger, D. M., Tchetgen Tchetgen, E. & Scott, J. A. G. (2012). Estimating rates of carriage acquisition and clearance and competitive ability for pneumococcal serotypes in kenya with a markov transition model. *Epidemiology*, 23(4), 510–519.

- Lipsitch, M., Colijn, C., Cohen, T., Hanage, W. P. & Fraser, C. (2009). No coexistence for free: Neutral null models for multistrain pathogens. *Epidemics*, *1*(1), 2–13.
- Lipsitch, M. & O’Hagan, J. J. (2007). Patterns of antigenic diversity and the mechanisms that maintain them. *J. R. Soc. Interface*, *4*(16), 787–802.
- Liu, J. Z. & Anderson, C. A. (2014). Genetic studies of crohn’s disease: Past, present and future. *Best Practice and Research: Clinical Gastroenterology*, *28*(3), 373–386.
- Llull, D., Muñoz, R., López, R. & Garcia, E. (1999). A single gene (tts) located outside the cap locus directs the formation of streptococcus pneumoniae type 37 capsular polysaccharide. *J. Exp. Med.* *190*(2), 241–252.
- Lockhart, R., Taylor, J., Tibshirani, R. J. & Tibshirani, R. (2014). A significance test for the lasso. *Ann. Stat.* *42*(2), 413–468.
- Loeffler, J. M. & Fischetti, V. A. (2006). Lysogeny of streptococcus pneumoniae with MM1 phage: Improved adherence and other phenotypic changes. *Infect. Immun.* *74*(8), 4486–4495.
- Loh, P.-R., Danecek, P., Palamara, P. F., Fuchsberger, C., A Reshef, Y., K Finucane, H., ... L Price, A. (2016). Reference-based phasing using the haplotype reference consortium panel. *Nat. Genet.* *48*(11), 1443–1448.
- Loh, P.-R., Tucker, G., Bulik-Sullivan, B. K., Vilhjálmsón, B. J., Finucane, H. K., Salem, R. M., ... Price, A. L. (2015). Efficient bayesian mixed-model analysis increases association power in large cohorts. *Nat. Genet.* *47*(3), 284–290.
- Lund, E. & Henrichsen, J. (1978). Chapter XI laboratory diagnosis, serology and epidemiology of streptococcus pneumoniae. *Methods in Microbiology*, *12*, 241–262.
- Luo, Y., de Lange, K. M., Jostins, L., Moutsianas, L., Randall, J., Kennedy, N. A., ... Anderson, C. A. (2017). Exploring the genetic architecture of inflammatory bowel disease by whole-genome sequencing identifies association at ADCY7. *Nat. Genet.* *49*(2), 186–192.
- Lutz, S. M., Cho, M. H., Young, K., Hersh, C. P., Castaldi, P. J., McDonald, M.-L., ... COPDGene Investigators. (2015). A genome-wide association study identifies risk loci for spirometric measures among smokers of european and african ancestry. *BMC Genet.* *16*, 138.
- Lynch, M. & Walsh, B. (1998). *Genetics and analysis of quantitative traits* (1998 edition). Sinauer.
- Lysenko, E. S., Ratner, A. J., Nelson, A. L. & Weiser, J. N. (2005). The role of innate immune responses in the outcome of interspecies competition for colonization of mucosal surfaces. *PLoS Pathog.* *1*(1), e1.
- MacArthur, J., Bowler, E., Cerezo, M., Gil, L., Hall, P., Hastings, E., ... Parkinson, H. (2017). The new NHGRI-EBI catalog of published genome-wide association studies (GWAS catalog). *Nucleic Acids Res.* *45*(D1), D896–D901.

- Magnusson, M., Tobes, R., Sancho, J. & Pareja, E. (2007). Cutting edge: Natural DNA repetitive extragenic sequences from Gram-Negative pathogens strongly stimulate TLR9. *The Journal of Immunology*, *179*(1), 31–35.
- Magoc, T., Pabinger, S., Canzar, S., Liu, X., Su, Q., Puiu, D., ... Salzberg, S. L. (2013). GAGE-B: An evaluation of genome assemblers for bacterial organisms. *Bioinformatics*, *29*(14), 1718–1725.
- Mahdi, L. K., Van der Hoek, M. B., Ebrahimie, E., Paton, J. C. & Ogunniyi, A. D. (2015). Characterization of pneumococcal genes involved in bloodstream invasion in a mouse model. *PLoS One*, *10*(11), e0141816.
- Mai, N. T. H., Chau, T. T. H., Thwaites, G., Chuong, L. V., Sinh, D. X., Nghia, H. D. T., ... Farrar, J. J. (2007). Dexamethasone in vietnamese adolescents and adults with bacterial meningitis. *N. Engl. J. Med.* *357*(24), 2431–2440.
- Maiden, M., Bygraves, J. A., Feil, E., Morelli, G., Russell, J. E., Urwin, R., ... Spratt, B. G. (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*(6), 3140–3145.
- Manco, S., Hernon, F., Yesilkaya, H., Paton, J. C., Andrew, P. W. & Kadioglu, A. (2006). Pneumococcal neuraminidases a and B both have essential roles during infection of the respiratory tract and sepsis. *Infect. Immun.* *74*(7), 4014–4020.
- Manichaikul, A., Mychaleckyj, J. C., Rich, S. S., Daly, K., Sale, M. & Chen, W.-M. (2010). Robust relationship inference in genome-wide association studies. *Bioinformatics*, *26*(22), 2867–2873.
- Manolio, T. A., Collins, F. S., Cox, N. J., Goldstein, D. B., Hindorff, L. A., Hunter, D. J., ... Visscher, P. M. (2009). Finding the missing heritability of complex diseases. *Nature*, *461*(7265), 747–753.
- Manso, A. S., Chai, M. H., Atack, J. M., Furi, L., De Ste Croix, M., Haigh, R., ... Oggioni, M. R. (2014). A random six-phase switch regulates pneumococcal virulence via global epigenetic changes. *Nat. Commun.* *5*, 5055.
- Maródi, L. (2006). Neonatal innate immunity to infectious agents. *Infect. Immun.* *74*(4), 1999–2006.
- Marschall, T., Marz, M., Abeel, T., Dijkstra, L., Dutilh, B. E., Ghaffaari, A., ... Schoenhuth, A. (2016). *Computational Pan-Genomics: Status, promises and challenges*.
- Martins, E. P. & Garland, T. (1991). Phylogenetic analyses of the correlated evolution of continuous characters: A simulation study. *Evolution*, *45*(3), 534–557.
- Marttinen, P. & Corander, J. (2010). Efficient bayesian approach for multilocus association mapping including gene-gene interactions. *BMC Bioinformatics*, *11*, 443.
- Marttinen, P., Gillberg, J., Havulinna, A., Corander, J. & Kaski, S. (2013). Genome-wide association studies with high-dimensional phenotypes. *Stat. Appl. Genet. Mol. Biol.* *12*(4), 413–431.

- Marttinen, P., Pirinen, M., Sarin, A.-P., Gillberg, J., Kettunen, J., Surakka, I., ... Kaski, S. (2014). Assessing multivariate gene-metabolome associations with rare variants using bayesian reduced rank regression. *Bioinformatics*, 30(14), 2026–2034.
- Marvig, R. L., Sommer, L. M., Molin, S. & Johansen, H. K. (2014). Convergent evolution and adaptation of *Pseudomonas aeruginosa* within patients with cystic fibrosis. *Nat. Genet.* 47(1), 57–64.
- Maskell, J. P., Sefton, a. M. & Hall, L. M. C. (2001). Multiple mutations modulate the function of dihydrofolate reductase in trimethoprim-resistant *Streptococcus pneumoniae*. *Antimicrob. Agents Chemother.* 45(4), 1104–1108.
- Maury, M., Tsai, Y.-H., Charlier, C., Touchon, M., Chenal-Francisque, V., Leclercq, A., ... Lecuit, M. (2016). Uncovering *Listeria monocytogenes* hypervirulence by harnessing its biodiversity. *Nat. Genet.* 48(3), 308–313.
- McCarthy, S., Das, S., Kretzschmar, W., Delaneau, O., Wood, A. R., Teumer, A., ... Marchini, J. (2016). A reference panel of 64,976 haplotypes for genotype imputation. *Nat. Genet.*
- McCool, T. L., Cate, T. R., Moy, G. & Weiser, J. N. (2002). The immune response to pneumococcal proteins during experimental human carriage. *J. Exp. Med.* 195(3), 359–365.
- McCullers, J. A. (2006). Insights into the interaction between influenza virus and pneumococcus. *Clin. Microbiol. Rev.* 19(3), 571–582.
- McCulloch, C. E. (2003). Chapter 4: Generalized linear mixed models (GLMMs). In *Generalized linear mixed models* (pp. 28–33). IMS and ASA.
- McInerney, J. O., McNally, A. & O’Connell, M. J. (2017). Why prokaryotes have pangenomes. *Nature Microbiology*, 2, 17040.
- McIntyre, P. B., O’Brien, K. L., Greenwood, B. & van de Beek, D. (2012). Effect of vaccines on bacterial meningitis worldwide. *Lancet*, 380(9854), 1703–1711.
- McLaren, W., Pritchard, B., Rios, D., Chen, Y., Flicek, P. & Cunningham, F. (2010). Deriving the consequences of genomic variants with the ensembl API and SNP effect predictor. *Bioinformatics*, 26(16), 2069–2070.
- McNeil, L. K., Zagursky, R. J., Lin, S. L., Murphy, E., Zlotnick, G. W., Hoiseth, S. K., ... Anderson, A. S. (2013). Role of factor H binding protein in *Neisseria meningitidis* virulence and its potential as a vaccine candidate to broadly protect against meningococcal disease. *Microbiol. Mol. Biol. Rev.* 77(2), 234–252.
- Melegaro, A., Choi, Y., Pebody, R. & Gay, N. (2007). Pneumococcal carriage in united kingdom families: Estimating serotype-specific transmission parameters from longitudinal data. *Am. J. Epidemiol.* 166(2), 228–235.
- Melin, M., Trzcinski, K., Meri, S., Käyhty, H. & Väkeväinen, M. (2010). The capsular serotype of *Streptococcus pneumoniae* is more important than the genetic background for resistance to complement. *Infect. Immun.* 78(12), 5262–5270.

- Miller, E., Kjos, M., Abrudan, M., Roberts, I. S., Veening, J.-W. & Rozen, D. (2017). *Crosstalk and eavesdropping among quorum sensing peptide signals that regulate bacteriocin production in streptococcus pneumoniae*.
- Mitov, V. & Stadler, T. (2016). The heritability of pathogen traits - definitions and estimators. *bioRxiv*, 1–46.
- Mohedano, M. L., Overweg, K., de la Fuente, A., Reuter, M., Altabe, S., Mulholland, F., ... Wells, J. M. (2005). Evidence that the essential response regulator YycF in streptococcus pneumoniae modulates expression of fatty acid biosynthesis genes and alters membrane composition. *J. Bacteriol.* 187(7), 2357–2367.
- Moll, G., Ubbink-Kok, T., Hildeng-Hauge, H., Nissen-Meyer, J., Nes, I. F., Konings, W. N. & Driessen, A. J. (1996). Lactococcin G is a potassium ion-conducting, two-component bacteriocin. *J. Bacteriol.* 178(3), 600–605.
- Molyneux, E., Walsh, A., Forsyth, H., Tembo, M., Mwenechanya, J., Kayira, K., ... Malenga, G. (2002). Dexamethasone treatment in childhood bacterial meningitis in malawi: A randomised controlled trial. *Lancet*, 360(9328), 211–218.
- Molzen, T. E., Burghout, P., Bootsma, H. J., Brandt, C. T., Der Gaast-De Jongh, C. E. V., Eleveld, M. J., ... Hermans, P. W. M. (2011). Genome-wide identification of streptococcus pneumoniae genes essential for bacterial replication during experimental meningitis. *Infect. Immun.* 79(1), 288–297.
- Molzen, T. E., Burghout, P., Bootsma, H. J., Brandt, C. T., van der Gaast-de Jongh, C. E., Eleveld, M. J., ... Hermans, P. W. M. (2011). Genome-wide identification of streptococcus pneumoniae genes essential for bacterial replication during experimental meningitis. *Infect. Immun.* 79(1), 288–297.
- Monitoring Reports SHM. (2013). <https://www.hiv-monitoring.nl/english/research/monitoringreports/>. Accessed: 2017-6-1.
- Mook-Kanamori, B. B., Geldhoff, M., van der Poll, T. & van de Beek, D. (2011). Pathogenesis and pathophysiology of pneumococcal meningitis. *Clin. Microbiol. Rev.* 24(3), 557–591.
- Morelli, G., Didelot, X., Kusecek, B., Schwarz, S., Bahlawane, C., Falush, D., ... Achtman, M. (2010). Microevolution of helicobacter pylori during prolonged infection of single hosts and within families. *PLoS Genet.* 6(7), e1001036.
- Morris, A. P. & Zeggini, E. (2010). An evaluation of statistical approaches to rare variant analysis in genetic association studies. *Genet. Epidemiol.* 34(2), 188–193.
- Morton, N. E. (1955). Sequential tests for the detection of linkage. *Am. J. Hum. Genet.* 7(3), 277–318.
- Mostowy, R., Croucher, N. J., Andam, C. P., Corander, J., Hanage, W. P. & Marttinen, P. (2017). Efficient inference of recent and ancestral recombination within bacterial populations. *Mol. Biol. Evol.* 34(5), 1167–1182.

- Moxon, E. R. & Murphy, P. A. (1978). Haemophilus influenzae bacteremia and meningitis resulting from survival of a single organism. *Proc. Natl. Acad. Sci. U. S. A.* 75(3), 1534–1536.
- Moxon, E. R., Rainey, P. B., Nowak, M. A. & Lenski, R. E. (1994). Adaptive evolution of highly mutable loci in pathogenic bacteria. *Curr. Biol.* 4(1), 24–33.
- Musher, D. M. (1992). Infections caused by streptococcus pneumoniae: Clinical spectrum, pathogenesis, immunity, and treatment. *Clin. Infect. Dis.* 14(4), 801–807.
- Mwangi, M. M., Wu, S. W., Zhou, Y., Sieradzki, K., de Lencastre, H., Richardson, P., ... Tomasz, A. (2007). Tracking the in vivo evolution of multidrug resistance in staphylococcus aureus by whole-genome sequencing. *Proc. Natl. Acad. Sci. U. S. A.* 104(22), 9451–9456.
- Nadeem Khan, M., Coleman, J. R., Vernatter, J., Varshney, A. K., Dufaud, C. & Pirofski, L.-A. (2014). An ahemolytic pneumolysin of streptococcus pneumoniae manipulates human innate and CD4+ t-cell responses and reduces resistance to colonization in mice in a serotype-independent manner. *J. Infect. Dis.* 210(10), 1658–1669.
- Nebenzahl-Guimaraes, H., van Laarhoven, A., Farhat, M. R., Koeken, V. A., Mandemakers, J. J., Zomer, A., ... van Soolingen, D. (2016). Transmissible mycobacterium tuberculosis strains share genetic markers and immune phenotypes. *Am. J. Respir. Crit. Care Med.*
- Newman, S. C. (2003). Appendix d: Quadratic equation for the odds ratio. In *Biostatistical methods in epidemiology* (pp. 329–330). John Wiley & Sons, Inc.
- Newport, M. J. & Finan, C. (2011). Genome-wide association studies and susceptibility to infectious diseases. *Brief. Funct. Genomics*, 10(2), 98–107.
- Ng, P. C. & Henikoff, S. (2003). SIFT: Predicting amino acid changes that affect protein function. *Nucleic Acids Res.* 31(13), 3812–3814.
- Nigrovic, L. E., Malley, R., Macias, C. G., Kanegaye, J. T., Moro-Sutherland, D. M., Schremmer, R. D., ... American Academy of Pediatrics, Pediatric Emergency Medicine Collaborative Research Committee. (2008). Effect of antibiotic pretreatment on cerebrospinal fluid profiles of children with bacterial meningitis. *Pediatrics*, 122(4), 726–730.
- Numminen, E., Cheng, L., Gyllenberg, M. & Corander, J. (2013). Estimating the transmission dynamics of streptococcus pneumoniae from strain prevalence data. *Biometrics*, 69(3), 748–757.
- Obaro, S. K., Adegbola, R. A., Banya, W. & Greenwood, B. M. (1996). Carriage of pneumococci after pneumococcal vaccination. *Lancet*, 348(9022), 271–272.
- Obert, C., Sublett, J., Kaushal, D., Hinojosa, E., Barton, T., Tuomanen, E. I. & Orihuela, C. J. (2006). Identification of a candidate streptococcus pneumoniae core genome and regions of diversity correlated with invasive pneumococcal disease. *Infect. Immun.* 74(8), 4766–4777.

- Ochman, H., Elwyn, S. & Moran, N. A. (1999). Calibrating bacterial evolution. *Proceedings of the National Academy of Sciences*, 96(22), 12638–12643.
- O’Connell, J., Gurdasani, D., Delaneau, O., Pirastu, N., Ulivi, S., Cocca, M., . . . Marchini, J. (2014). A general approach for haplotype phasing across the full spectrum of relatedness. *PLoS Genet.* 10(4), e1004234.
- Ogunniyi, A. D., LeMessurier, K. S., Graham, R. M. A., Watt, J. M., Briles, D. E., Stroehler, U. H. & Paton, J. C. (2007). Contributions of pneumolysin, pneumococcal surface protein a (PspA), and PspC to pathogenicity of streptococcus pneumoniae D39 in a mouse model. *Infect. Immun.* 75(4), 1843–1851.
- Oliver, W. J., Shope, T. C. & Kuhns, L. R. (2003). Fatal lumbar puncture: Fact versus fiction—an approach to a clinical dilemma. *Pediatrics*, 112(3 Pt 1), e174–6.
- Omer, H., Rose, G., Jolley, K. a., Frapy, E., Zahar, J. R., Maiden, M., . . . Bille, E. (2011). Genotypic and phenotypic modifications of neisseria meningitidis after an accidental human passage. *PLoS One*, 6(2).
- Ondov, B. D., Treangen, T. J., Melsted, P., Mallonee, A. B., Bergman, N. H., Koren, S. & Phillippy, A. M. (2016). Mash: Fast genome and metagenome distance estimation using MinHash. *Genome Biol.* 17(1), 1–14.
- Ott, J., Wang, J. & Leal, S. M. (2015). Genetic linkage analysis in the age of whole-genome sequencing. *Nat. Rev. Genet.* 16(5), 275–284.
- Page, A. J., Cummins, C. A., Hunt, M., Wong, V. K., Reuter, S., Holden, M. T. G., . . . Parkhill, J. (2015). Roary: Rapid large-scale prokaryote pan genome analysis. *Bioinformatics*, 31(July), btv421.
- Page, A. J., De Silva, N., Hunt, M., Quail, M. A., Parkhill, J., Harris, S. R., . . . Keane, J. A. (2016). Robust high-throughput prokaryote de novo assembly and improvement pipeline for illumina data. *Microbial Genomics*, 2(8).
- Pagel, M. (1997). Inferring evolutionary processes from phylogenies. *Zool. Scr.* 26(4), 331–348.
- Park, I. H., Kim, K.-H., Andrade, A. L., Briles, D. E., McDaniel, L. S. & Nahm, M. H. (2012). Nontypeable pneumococci can be divided into multiple cps types, including one type expressing the novel gene pspk. *MBio*, 3(3).
- Paten, B., Earl, D., Nguyen, N., Diekhans, M., Zerbino, D. & Haussler, D. (2011). Cactus: Algorithms for genome multiple sequence alignment. *Genome Res.* 21(9), 1512–1528.
- Paten, B., Novak, A. M., Eizenga, J. M. & Garrison, E. (2017). Genome graphs and the evolution of genome inference. *Genome Res.* 27(5), 665–676.
- Paternoster, L., Evans, D. M., Aagaard Nohr, E., Holst, C., Gaborieau, V., Brennan, P., . . . Sørensen, T. I. A. (2011). Genome-Wide Population-Based association study of extremely overweight young adults – the GOYA study. *PLoS One*, 6(9), e24303.

- Paterson, G. K. & Mitchell, T. J. (2006). Innate immunity and the pneumococcus. *Microbiology*, 152(Pt 2), 285–293.
- Paterson, G. K., Nieminen, L., Jefferies, J. M. C. & Mitchell, T. J. (2008). PclA, a pneumococcal collagen-like protein with selected strain distribution, contributes to adherence and invasion of host cells. *FEMS Microbiol. Lett.* 285(2), 170–176.
- Paterson, G. K. & Orihuela, C. J. (2010). Pneumococci: Immunology of the innate host response. *Respirology*, 15(7), 1057–1063.
- Pathan, N., Faust, S. N. & Levin, M. (2003). Pathophysiology of meningococcal meningitis and septicaemia. *Arch. Dis. Child.* 88(7), 601–607.
- Patwa, Z. & Wahl, L. M. (2008). The fixation probability of beneficial mutations. *J. R. Soc. Interface*, 5(28), 1279–1289.
- Pericone, C. D., Overweg, K., Hermans, P. W. M. & Weiser, J. N. (2000). Inhibitory and bactericidal effects of hydrogen peroxide production by streptococcus pneumoniae on other inhabitants of the upper respiratory tract. *Infect. Immun.* 68(7), 3990–3997.
- Pickrell, J. K., Berisa, T., Liu, J. Z., Ségurel, L., Tung, J. Y. & Hinds, D. A. (2016). Detection and interpretation of shared genetic influences on 42 human traits. *Nat. Genet.* 48(7), 709–717.
- Piet, J. R., Geldhoff, M., Van Schaik, B. D. C., Brouwer, M. C., Valls Seron, M., Jakobs, M. E., . . . Van De Beek, D. (2014). Streptococcus pneumoniae arginine synthesis genes promote growth and virulence in pneumococcal meningitis. *J. Infect. Dis.* 209(11), 1781–1791.
- Pletz, M. W. R., Fugit, R. V., McGee, L., Glasheen, J. J., Keller, D. L., Welte, T. & Klugman, K. P. (2006). Fluoroquinolone-resistant streptococcus pneumoniae. *Emerg. Infect. Dis.* 12(9), 1462–1463.
- Plumtre, C. D., Ogunniyi, A. D. & Paton, J. C. (2013). Surface association of pht proteins of streptococcus pneumoniae. *Infect. Immun.* 81(10), 3644–3651.
- Poulsen, K., Reinholdt, J. & Kilian, M. (1996). Characterization of the streptococcus pneumoniae immunoglobulin A1 protease gene (iga) and its translation product. *Infect. Immun.* 64(10), 3957–3966.
- Power, R. A., Parkhill, J. & de Oliveira, T. (2016). Microbial genome-wide association studies: Lessons from human GWAS. *Nat. Rev. Genet.*
- Price, A. L., Patterson, N. J., Plenge, R. M., Weinblatt, M. E., Shadick, N. A. & Reich, D. (2006). Principal components analysis corrects for stratification in genome-wide association studies. *Nat. Genet.* 38(8), 904–909.
- Price, A. L., Zaitlen, N. A. [N A], Reich, D. & Patterson, N. (2010). New approaches to population stratification in genome-wide association studies. *Nat. Rev. Genet.* 11(7), 459–463.

- Price, A. L., Zaitlen, N. A. [Noah A], Reich, D. & Patterson, N. (2010). New approaches to population stratification in genome-wide association studies. *Nat. Rev. Genet.* 11(7), 459–463.
- Price, M. N., Dehal, P. S. & Arkin, A. P. (2009). Fasttree: Computing large minimum evolution trees with profiles instead of a distance matrix. *Mol. Biol. Evol.* 26(7), 1641–1650.
- Proulx, N., Fréchet, D., Toye, B., Chan, J. & Kravcik, S. (2005). Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. *QJM*, 98(4), 291–298.
- Pruim, R. J., Welch, R. P., Sanna, S., Teslovich, T. M., Chines, P. S., Gliedt, T. P., ... Willer, C. J. (2010). LocusZoom: Regional visualization of genome-wide association scan results. *Bioinformatics*, 26(18), 2336–2337.
- Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. a. R., Bender, D., ... Sham, P. C. (2007). PLINK: A tool set for whole-genome association and population-based linkage analyses. *Am. J. Hum. Genet.* 81(3), 559–575.
- Quinton, L. J., Jones, M. R., Simms, B. T., Kogan, M. S., Robson, B. E., Skerrett, S. J. & Mizgerd, J. P. (2007). Functions and regulation of NF-kappaB RelA during pneumococcal pneumonia. *J. Immunol.* 178(3), 1896–1903.
- Raeder, R. & Boyle, M. D. (1993). Association between expression of immunoglobulin g-binding proteins by group a streptococci and virulence in a mouse skin infection model. *Infect. Immun.* 61(4), 1378–1384.
- Raeder, R. & Boyle, M. D. (1995). Analysis of immunoglobulin g-binding-protein expression by invasive isolates of streptococcus pyogenes. *Clin. Diagn. Lab. Immunol.* 2(4), 484–486.
- Ragunathan, L., Ramsay, M., Borrow, R., Guiver, M., Gray, S. & Kaczmarski, E. B. (2000). Clinical features, laboratory findings and management of meningococcal meningitis in england and wales: Report of a 1997 survey. meningococcal meningitis: 1997 survey report. *J. Infect.* 40(1), 74–79.
- Rau, M. H., Marvig, R. L., Ehrlich, G. D., Molin, S. & Jelsbak, L. (2012). Deletion and acquisition of genomic content during early stage adaptation of pseudomonas aeruginosa to a human host environment. *Environ. Microbiol.* 14(8), 2200–2211.
- Rautanen, A., Pirinen, M., Mills, T. C., Rockett, K. A., Strange, A., Ndungu, A. W., ... Spencer, C. C. A. (2016). Polymorphism in a lincRNA associates with a doubled risk of pneumococcal bacteremia in kenyan children. *Am. J. Hum. Genet.* 2, 1092–1100.
- Read, A. F. & Nee, S. (1995). Inference from binary comparative data. *J. Theor. Biol.* 173(1), 99–108.
- Read, T. D. & Massey, R. C. (2014). Characterizing the genetic basis of bacterial phenotypes using genome-wide association studies: A new direction for bacteriology. *Genome Med.* 6(11), 109.

- Reddy, U. R., Phatak, S. & Pleasure, D. (1996). Human neural tissues express a truncated *ror1* receptor tyrosine kinase, lacking both extracellular and transmembrane domains. *Oncogene*, *13*(7), 1555–1559.
- Regev-Yochay, G., Trzcinski, K., Thompson, C. M., Malley, R. & Lipsitch, M. (2006). Interference between streptococcus pneumoniae and staphylococcus aureus: In vitro hydrogen peroxide-mediated killing by streptococcus pneumoniae. *J. Bacteriol.* *188*(13), 4996–5001.
- Reich, D. E., Cargill, M., Bolk, S., Ireland, J., Sabeti, P. C., Richter, D. J., . . . Lander, E. (2001). Linkage disequilibrium in the human genome. *Nature*, *411*(6834), 199–204.
- Revell, L. J. (2013). Two new graphical methods for mapping trait evolution on phylogenies. *Methods Ecol. Evol.* *4*(8), 754–759.
- Risch, N. & Merikangas, K. (1996). The future of genetic studies of complex human diseases. *Science*, *273*, 1516–1517.
- Rizk, G., Lavenier, D. & Chikhi, R. (2013). DSK: K-mer counting with very low memory usage. *Bioinformatics*, *29*(5), 652–653.
- Roberts, A. P. & Mullany, P. (2009). A modular master on the move: The *tn916* family of mobile genetic elements. *Trends Microbiol.* *17*(May), 251–258.
- Robinson, D. A., Edwards, K. M., Waites, K. B., Briles, D. E., Crain, M. J. & Hollingshead, S. K. (2001). Clones of streptococcus pneumoniae isolated from nasopharyngeal carriage and invasive disease in young children in central tennessee. *J. Infect. Dis.* *183*(10), 1501–1507.
- Robinson, M. W., Buchtman, K. A., Jenkins, C., Tacchi, J. L., Raymond, B. B. A., To, J., . . . Djordjevic, S. P. (2013). MHJ_0125 is an M42 glutamyl aminopeptidase that moonlights as a multifunctional adhesin on the surface of mycoplasma hyopneumoniae. *Open Biol.* *3*(4), 130017.
- Rodrigo, C., Bewick, T., Sheppard, C., Greenwood, S., Macgregor, V., Trotter, C., . . . Lim, W. S. (2014). Pneumococcal serotypes in adult non-invasive and invasive pneumonia in relation to child contact and child vaccination status. *Thorax*, *69*(2), 168–173.
- Romero, P., Croucher, N. J., Hiller, N. L., Hu, F. Z., Ehrlich, G. D., Bentley, S. D., . . . Mitchell, T. J. (2009). Comparative genomic analysis of ten streptococcus pneumoniae temperate bacteriophages. *J. Bacteriol.* *191*(15), 4854–4862.
- Rosenthal, R. (1978). Combining results of independent studies. *Psychol. Bull.* *85*(1), 185.
- Rouphael, N. G. & Stephens, D. S. (2012). Neisseria meningitidis: Biology, microbiology, and epidemiology. *Methods Mol. Biol.* *799*, 1–20.
- Rubins, J. B., Paddock, A. H., Charboneau, D., Berry, A. M., Paton, J. C. & Janoff, E. N. (1998). Pneumolysin in pneumococcal adherence and colonization. *Microb. Pathog.* *25*(6), 337–342.
- Russell, J. E., Jolley, K. a., Feavers, I. M., Maiden, M. & Suker, J. (2004). PorA variable regions of neisseria meningitidis. *Emerg. Infect. Dis.* *10*(4), 674–678.

- Sachidanandam, R., Weissman, D., Schmidt, S. C., Kakol, J. M., Stein, L. D., Marth, G., ... International SNP Map Working Group. (2001). A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. *Nature*, 409(6822), 928–933.
- Salipante, S. J., Roach, D. J., Kitzman, J. O., Snyder, M. W., Stackhouse, B., Butler-Wu, S. M., ... Shendure, J. (2015). Large-scale genomic sequencing of extraintestinal pathogenic escherichia coli strains. *Genome Res.* 25(1), 119–128.
- Salter, S. J., Hinds, J., Gould, K. A., Lambertsen, L., Hanage, W. P., Antonio, M., ... Bentley, S. D. (2012). Variation at the capsule locus, cps, of mistyped and non-typable streptococcus pneumoniae isolates. *Microbiology*, 158(Pt 6), 1560–1569.
- Samocha, K. E., Robinson, E. B., Sanders, S. J., Stevens, C., Sabo, A., McGrath, L. M., ... Daly, M. J. (2014). A framework for the interpretation of de novo mutation in human disease. *Nat. Genet.* 46(9), 944–950.
- Samore, M. H., Lipsitch, M., Alder, S. C., Haddadin, B., Stoddard, G., Williamson, J., ... Sande, M. a. (2006). Mechanisms by which antibiotics promote dissemination of resistant pneumococci in human populations. *Am. J. Epidemiol.* 163(2), 160–170.
- Sánchez-Beato, A. R., López, R. & García, J. L. (1998). Molecular characterization of PcpA: A novel choline-binding protein of streptococcus pneumoniae. *FEMS Microbiol. Lett.* 164(1), 207–214.
- Sanderson, C. (2010). Armadillo: An open source c++ linear algebra library for fast prototyping and computationally intensive experiments. In *NICTA* (Vol. NICTA, pp. 1–16). Australia.
- Sanderson, C. & Curtin, R. (2016). Armadillo: A template-based c++ library for linear algebra. *JOSS*, 1(2).
- Sarkari, J., Pandit, N., Moxon, E. R. & Achtman, M. (1994). Variable expression of the opc outer membrane protein in neisseria meningitidis is caused by size variation of a promoter containing poly-cytidine. *Mol. Microbiol.* 13(2), 207–217.
- Schraiber, J. G. & Akey, J. M. (2015). Methods and models for unravelling human evolutionary history. *Nat. Rev. Genet.* 16(12), 727–740.
- Schuchat, A., Robinson, K., Wenger, J. D., Harrison, L. H., Farley, M., Reingold, A. L., ... Perkins, B. A. (1997). Bacterial meningitis in the united states in 1995. active surveillance team. *N. Engl. J. Med.* 337(14), 970–976.
- Seale, A. C., Davies, M. R., Anampiu, K., Morpeth, S. C., Nyongesa, S., Mwarumba, S., ... Berkley, J. A. (2016). Invasive group a streptococcus infection among children, rural kenya. *Emerging Infectious Disease journal*, 22(2), 224.
- Serruto, D., Rappuoli, R., Scarselli, M., Gros, P. & van Strijp, J. A. G. (2010). Molecular mechanisms of complement evasion: Learning from staphylococci and meningococci. *Nat. Rev. Microbiol.* 8(6), 393–399.

- Seth, S., Välimäki, N., Kaski, S. & Honkela, A. (2014). Exploration and retrieval of whole-metagenome sequencing samples. *Bioinformatics*, 30(17), 16.
- Shah, T. S., Liu, J. Z., Floyd, J. a. B., Morris, J. a., Wirth, N., Barrett, J. C. & Anderson, C. a. (2012). Opticall: A robust genotype-calling algorithm for rare, low-frequency and common variants. *Bioinformatics*, 28(12), 1598–1603.
- Shakhnovich, E. A., King, S. J. & Weiser, J. N. (2002). Neuraminidase expressed by streptococcus pneumoniae desialylates the lipopolysaccharide of neisseria meningitidis and haemophilus influenzae: A paradigm for interbacterial competition among pathogens of the human respiratory tract. *Infect. Immun.* 70(12), 7161–7164.
- Shaper, M., Hollingshead, S. K., Benjamin, W. H., Jr & Briles, D. E. (2004). PspA protects streptococcus pneumoniae from killing by apolactoferrin, and antibody to PspA enhances killing of pneumococci by apolactoferrin. *Infect. Immun.* 72(9), 5031–5040.
- Shapiro, E. D. & Austrian, R. (1994). Serotypes responsible for invasive streptococcus pneumoniae infections among children in connecticut. *J. Infect. Dis.* 169(1), 212–214.
- Shea, P. R., Beres, S. B., Flores, A. R., Ewbank, A. L., Gonzalez-Lugo, J. H., Martagon-Rosado, A. J., ... Musser, J. M. (2011). Distinct signatures of diversifying selection revealed by genome analysis of respiratory tract and invasive bacterial populations. *Proc. Natl. Acad. Sci. U. S. A.* 108(12), 5039–5044.
- Sheppard, S. K., Didelot, X., Meric, G., Torralbo, A., Jolley, K. A., Kelly, D. J., ... Falush, D. (2013). Genome-wide association study identifies vitamin B5 biosynthesis as a host specificity factor in campylobacter. *Proceedings of the National Academy of Sciences*, 110(29), 11923–11927.
- Shivshankar, P., Sanchez, C., Rose, L. F. & Orihuela, C. J. (2009). The streptococcus pneumoniae adhesin PsrP binds to keratin 10 on lung cells. *Mol. Microbiol.* 73(4), 663–679.
- Siddique, T., Figlewicz, D. A., Pericak-Vance, M. A., Haines, J. L., Rouleau, G., Jeffers, A. J., ... McKenna-Yasek, D. (1991). Linkage of a gene causing familial amyotrophic lateral sclerosis to chromosome 21 and evidence of genetic-locus heterogeneity. *N. Engl. J. Med.* 324(20), 1381–1384.
- Siegel, S. J., Roche, A. M. & Weiser, J. N. (2014). Influenza promotes pneumococcal growth during coinfection by providing host sialylated substrates as a nutrient source. *Cell Host Microbe*, 16(1), 55–67.
- Simpson, J. T. & Durbin, R. (2012). Efficient de novo assembly of large genomes using compressed data structures. *Genome Res.* 22(3), 549–556.
- Skwark, M. J., Croucher, N. J., Puranen, S., Chewapreecha, C., Pesonen, M., Xu, Y. Y., ... Corander, J. (2017). Interacting networks of resistance, virulence and core machinery genes identified by genome-wide epistasis analysis. *PLoS Genet.* 13(2), e1006508.

- Smith, E. E., Buckley, D. G., Wu, Z., Saenphimmachak, C., Hoffman, L. R., D'Argenio, D. A., ... Olson, M. V. (2006). Genetic adaptation by *Pseudomonas aeruginosa* to the airways of cystic fibrosis patients. *Proceedings of the National Academy of Sciences*, *103*(22), 8487–8492.
- Smith, T. C., Sledjeski, D. D. & Boyle, M. D. P. (2003a). Regulation of protein H expression in M1 serotype isolates of *Streptococcus pyogenes*. *FEMS Microbiol. Lett.* *219*(1), 9–15.
- Smith, T. C., Sledjeski, D. D. & Boyle, M. D. P. (2003b). *Streptococcus pyogenes* infection in mouse skin leads to a Time-Dependent Up-Regulation of protein H expression. *Infect. Immun.* *71*(10), 6079–6082.
- Snelson, E., Ghahramani, Z. & Rasmussen, C. E. (2004). Warped gaussian processes. In S. Thrun, L. K. Saul & P. B. Schölkopf (Eds.), *Advances in neural information processing systems 16* (pp. 337–344). MIT Press.
- Snyder, L. A. S., Saunders, N. J. & Shafer, W. M. (2001). A putatively phase variable gene (*dca*) required for natural competence in *Neisseria gonorrhoeae* but not *Neisseria meningitidis* is located within the division cell wall (*dcw*) gene cluster. *J. Bacteriol.* *183*(4), 1233–1241.
- Snyder, L. A. S., Shafer, W. M. & Saunders, N. J. (2003). Divergence and transcriptional analysis of the division cell wall (*dcw*) gene cluster in *Neisseria* spp. *Mol. Microbiol.* *47*(2), 431–442.
- Spain, S. L. & Barrett, J. C. (2015). Strategies for fine-mapping complex traits. *Hum. Mol. Genet.* *24*(R1), R111–R119.
- Speed, D., Cai, N., UCLEB Consortium, Johnson, M. R., Nejentsev, S. & Balding, D. J. (2017). Reevaluation of SNP heritability in complex human traits. *Nat. Genet.*
- Speed, D., Hemani, G., Johnson, M. R. & Balding, D. J. (2012). Improved heritability estimation from genome-wide SNPs. *Am. J. Hum. Genet.* *91*(6), 1011–1021.
- Spiegelhalter, D. J., Best, N. G., Carlin, B. P. & van der Linde, A. (2002). Bayesian measures of model complexity and fit. *J. R. Stat. Soc. Series B Stat. Methodol.* *64*(4), 583–639.
- Spielman, R. S., McGinnis, R. E. & Ewens, W. J. (1993). Transmission test for linkage disequilibrium: The insulin gene region and insulin-dependent diabetes mellitus (IDDM). *Am. J. Hum. Genet.* *52*(3), 506–516.
- Spijkerman, J., van Gils, E. J. M., Veenhoven, R. H., Hak, E., Yzerman, E. P. F., van der Ende, A., ... Sanders, E. A. M. (2011). Carriage of *Streptococcus pneumoniae* 3 years after start of vaccination program, the Netherlands. *Emerg. Infect. Dis.* *17*(4), 584–591.
- Spratt, B. G. (1994a). Chapter 25: Resistance to β -lactam antibiotics. *New Compr. Biochem.* *27*, 517–534.

- Spratt, B. G. (1994b). Resistance to antibiotics mediated by target alterations. *Science*, 264(5157), 388–393.
- Sreevatsan, S., Pan, X., Zhang, Y., Deretic, V. & Musser, J. M. (1997). Analysis of the oxyR-ahpC region in isoniazid-resistant and -susceptible mycobacterium tuberculosis complex organisms recovered from diseased humans and animals in diverse localities. *Antimicrob. Agents Chemother.* 41(3), 600–606.
- Stamatakis, A. (2014). RAxML version 8: A tool for phylogenetic analysis and post-analysis of large phylogenies. *Bioinformatics*, 30(9), 1312–1313.
- Steer, A. C., Magor, G., Jenney, A. W. J., Kado, J., Good, M. F., McMillan, D., ... Carapetis, J. R. (2009). Emm and c-repeat region molecular typing of beta-hemolytic streptococci in a tropical country: Implications for vaccine development. *J. Clin. Microbiol.* 47(8), 2502–2509.
- Stegle, O., Parts, L., Piipari, M., Winn, J. & Durbin, R. (2012). Using probabilistic estimation of expression residuals (PEER) to obtain increased power and interpretability of gene expression analyses. *Nat. Protoc.* 7(3), 500–507.
- Stessman, H. A. F., Xiong, B., Coe, B. P., Wang, T., Hoekzema, K., Fenckova, M., ... Eichler, E. E. (2017). Targeted sequencing identifies 91 neurodevelopmental-disorder risk genes with autism and developmental-disability biases. *Nat. Genet.* 49(4), 515–526.
- Stranger, B. E., Stahl, E. A. & Raj, T. (2011). Progress and promise of genome-wide association studies for human complex trait genetics. *Genetics*, 187(2), 367–383.
- Sveinbjornsson, G., Gudbjartsson, D. F., Halldorsson, B. V., Kristinsson, K. G., Gottfredsson, M., Barrett, J. C., ... Stefansson, K. (2016). HLA class II sequence variants influence tuberculosis risk in populations of european ancestry. *Nat. Genet.* 48(3), 318–322.
- Tajima, F. (1989). Statistical method for testing the neutral mutation hypothesis by DNA polymorphism. *Genetics*, 123(3), 585–595.
- Takahashi, H., Hirose, K. & Watanabe, H. (2004). Necessity of meningococcal gamma-glutamyl aminopeptidase for neisseria meningitidis growth in rat cerebrospinal fluid (CSF) and CSF-Like medium. *J. Bacteriol.* 186(1), 244–247.
- Takashima, K., Tateda, K., Matsumoto, T., Iizawa, Y., Nakao, M. & Yamaguchi, K. (1997). Role of tumor necrosis factor alpha in pathogenesis of pneumococcal pneumonia in mice. *Infect. Immun.* 65(1), 257–260.
- Tamayo, R., Pratt, J. T. & Camilli, A. (2007). Roles of cyclic diguanylate in the regulation of bacterial pathogenesis. *Annu. Rev. Microbiol.* 61, 131–148.
- Tasoulis, S., Cheng, L., Valimaki, N., Croucher, N. J., Harris, S. R., Hanage, W. P., ... Corander, J. (2014). Random projection based clustering for population genomics. In *2014 IEEE international conference on big data (big data)* (pp. 675–682).

- Tenaillon, O., Barrick, J. E., Ribeck, N., Deatherage, D. E., Blanchard, J. L., Dasgupta, A., ... Lenski, R. E. (2016). Tempo and mode of genome evolution in a 50,000-generation experiment. *Nature*, 536(7615), 165–170.
- Tettelin, H., Nelson, K. E., Paulsen, I. T., Eisen, J. a., Read, T. D., Peterson, S., ... Fraser, C. M. (2001). Complete genome sequence of a virulent isolate of streptococcus pneumoniae. *Science*, 293(5529), 498–506.
- Tettelin, H., Saunders, N. J., Heidelberg, J., Jeffries, a. C., Nelson, K. E., Eisen, J. a., ... Venter, J. C. (2000). Complete genome sequence of neisseria meningitidis serogroup B strain MC58. *Science*, 287(5459), 1809–1815.
- The Genome of the Netherlands Consortium. (2014). Whole-genome sequence variation, population structure and demographic history of the dutch population. *Nat. Genet.* 46(8), 818–825.
- Thorpe, H. A., Bayliss, S. C., Hurst, L. D. & Feil, E. J. (2017). Comparative analyses of selection operating on nontranslated intergenic regions of diverse bacterial species. *Genetics*, 206(1), 363–376.
- Tian, C., Hinds, D. A., Hromatka, B. S., Kiefer, A. K., Eriksson, N. & Tung, J. Y. (2016). *Genome-wide association and HLA region fine-mapping studies identify susceptibility loci for multiple common infections.*
- Tibshirani, R., Walther, G. & Hastie, T. (2001). Estimating the number of clusters in a data set via the gap statistic. *J. R. Stat. Soc. Series B Stat. Methodol.* 63(2), 411–423.
- Trappetti, C., McAllister, L. J., Chen, A., Wang, H., Paton, A. W., Oggioni, M. R., ... Paton, J. C. (2017). Autoinducer 2 signaling via the phosphotransferase FruA drives galactose utilization by streptococcus pneumoniae, resulting in hypervirulence. *MBio*, 8(1).
- Treangen, T. J., Ondov, B. D., Koren, S. & Phillippy, A. M. (2014). The harvest suite for rapid core-genome alignment and visualization of thousands of intraspecific microbial genomes. *Genome Biol.* 15(11), 524.
- Trzciński, K., Li, Y., Weinberger, D. M., Thompson, C. M., Cordy, D., Bessolo, A., ... Lipsitch, M. (2015). Effect of serotype on pneumococcal competition in a mouse colonization model. *MBio*, 6(5), e00902–15.
- Tu, A. H., Fulgham, R. L., McCrory, M. A., Briles, D. E. & Szalai, A. J. (1999). Pneumococcal surface protein a inhibits complement activation by streptococcus pneumoniae. *Infect. Immun.* 67(9), 4720–4724.
- Tunjungputri, R. N., Mobegi, F. M., Cremers, A. J., van der Gaast-de Jongh, C. E., Ferwerda, G., Meis, J. F., ... de Jonge, M. I. (2017). Phage-Derived protein induces increased platelet activation and is associated with mortality in patients with invasive pneumococcal disease. *MBio*, 8(1).
- Tunkel, A. R. & Scheld, W. M. (2002). Treatment of bacterial meningitis. *Curr. Infect. Dis. Rep.* 4(1), 7–16.

- Turner, C., Turner, P., Carrara, V., Burgoine, K., Htoo, S. T. L., Watthanaworawit, W., . . . Nosten, F. (2013). High rates of pneumonia in children under two years of age in a south east asian refugee population. *PLoS One*, 8(1), e54026.
- Turner, P., Turner, C., Jankhot, A., Helen, N., Lee, S. J., Day, N. P., . . . Goldblatt, D. (2012). A longitudinal study of streptococcus pneumoniae carriage in a cohort of infants and their mothers on the Thailand-Myanmar border. *PLoS One*, 7(5).
- Turner, P., Turner, C., Jankhot, A., Phakaudom, K., Nosten, F. & Goldblatt, D. (2013). Field evaluation of culture plus latex sweep serotyping for detection of multiple pneumococcal serotype colonisation in infants and young children. *PLoS One*, 8(7), 1–7.
- Unemo, M. & Shafer, W. M. (2014). Antimicrobial resistance in neisseria gonorrhoeae in the 21st century: Past, evolution, and future. *Clin. Microbiol. Rev.* 27(3), 587–613.
- Uricaru, R., Rizk, G., Lacroix, V., Quillery, E., Plantard, O., Chikhi, R., . . . Peterlongo, P. (2014). Reference-free detection of isolated SNPs. *Nucleic Acids Res.* 33(0), 1–11.
- Välimäki, N. & Puglisi, S. (2012). Distributed string mining for High-Throughput sequencing data. In B. Raphael & J. Tang (Eds.), *Algorithms in bioinformatics SE - 35* (Vol. 7534, pp. 441–452). Lecture Notes in Computer Science. Springer Berlin Heidelberg.
- van de Beek, D., de Gans, J., Spanjaard, L., Weisfelt, M., Reitsma, J. B. & Vermeulen, M. (2004). Clinical features and prognostic factors in adults with bacterial meningitis. *N. Engl. J. Med.* 351(18), 1849–1859.
- van de Beek, D., de Gans, J., Tunkel, A. R. & Wijdicks, E. F. M. (2006). Community-Acquired bacterial meningitis in adults. *N. Engl. J. Med.* 354(1), 44–53.
- van de Beek, D., Farrar, J. J., de Gans, J., Mai, N. T. H., Molyneux, E. M., Peltola, H., . . . Zwinderman, A. H. (2010). Adjunctive dexamethasone in bacterial meningitis: A meta-analysis of individual patient data. *Lancet Neurol.* 9(3), 254–263.
- Van der Auwera, G. A., Carneiro, M. O., Hartl, C., Poplin, R., del Angel, G., Levy-Moonshine, A., . . . DePristo, M. A. (2002). From FastQ data to High-Confidence variant calls: The genome analysis toolkit best practices pipeline. In *Current protocols in bioinformatics*. John Wiley & Sons, Inc.
- van der Ende, A., Hopman, C. T., Zaat, S., Essink, B. B., Berkhout, B. & Dankert, J. (1995). Variable expression of class 1 outer membrane protein in neisseria meningitidis is caused by variation in the spacing between the -10 and -35 regions of the promoter. *J. Bacteriol.* 177(9), 2475–2480.
- van der Ende, A., Hopman, C. T. P. & Dankert, J. (2000). Multiple mechanisms of phase variation of PorA in neisseria meningitidis. *Infect. Immun.* 68(12), 6685–6690.
- van Es, M. a., Veldink, J. H., Saris, C. G. J., Blauw, H. M., van Vught, P. W. J., Birve, A., . . . van den Berg, L. H. (2009). Genome-wide association study identifies 19p13.3

- (UNC13A) and 9p21.2 as susceptibility loci for sporadic amyotrophic lateral sclerosis. *Nat. Genet.* 41(10), 1083–1087.
- van Opijnen, T., Bodi, K. L. & Camilli, A. (2009). Tn-seq: High-throughput parallel sequencing for fitness and genetic interaction studies in microorganisms. *Nat. Methods*, 6(10), 767–772.
- van Veen, M. G., Presanis, A. M., Conti, S., Xiridou, M., Stengaard, A. R., Donoghoe, M. C., ... De Angelis, D. (2011). National estimate of HIV prevalence in the netherlands: Comparison and applicability of different estimation tools. *AIDS*, 25(2), 229–237.
- van Wijngaarden, J. P., Dhonukshe-Rutten, R. a. M., van Schoor, N. M., van der Velde, N., Swart, K. M. a., Enneman, A. W., ... de Groot, L. C. P. G. M. (2011). Rationale and design of the B-PROOF study, a randomized controlled trial on the effect of supplemental intake of vitamin B12 and folic acid on fracture incidence. *BMC Geriatr.* 11(1), 80.
- Veyrier, F. J., Boneca, I. G., Cellier, M. F. & Taha, M. K. (2011). A novel metal transporter mediating manganese export (mntx) regulates the mn to fe intracellular ratio and neisseria meningitidis virulence. *PLoS Pathog.* 7(9).
- Visscher, P. M., Hill, W. G. & Wray, N. R. (2008). Heritability in the genomics era—concepts and misconceptions. *Nat. Rev. Genet.* 9(4), 255–266.
- Vitányi, P. M. B., Balbach, F. J., Cilibiasi, R. L. & Li, M. (2009). Normalized information distance. *Information Theory and Statistical Learning*, 45–82.
- Walker, M. J., Barnett, T. C., McArthur, J. D., Cole, J. N., Gillen, C. M., Henningham, A., ... Nizet, V. (2014). Disease manifestations and pathogenic mechanisms of group a streptococcus. *Clin. Microbiol. Rev.* 27(2), 264–301.
- Walport, M. J. (2001a). Complement. first of two parts. *N. Engl. J. Med.* 344(14), 1058–1066.
- Walport, M. J. (2001b). Complement. second of two parts. *N. Engl. J. Med.* 344(15), 1140–1144.
- Wang, Z., Gerstein, M. & Snyder, M. (2009). RNA-Seq: A revolutionary tool for transcriptomics. *Nat. Rev. Genet.* 10(1), 57–63.
- Wani, J. H., Gilbert, J. V., Plaut, A. G. & Weiser, J. N. (1996). Identification, cloning, and sequencing of the immunoglobulin A1 protease gene of streptococcus pneumoniae. *Infect. Immun.* 64(10), 3967–3974.
- Ward, N. & Moreno-Hagelsieb, G. (2014). Quickly finding orthologs as reciprocal best hits with BLAT, LAST, and UBLAST: How much do we miss? *PLoS One*, 9(7), e101850.
- Wartha, F., Beiter, K., Albiger, B., Fernebro, J., Zychlinsky, A., Normark, S. & Henriques-Normark, B. (2007). Capsule and d-alanylated lipoteichoic acids protect streptococ-

- cus pneumoniae against neutrophil extracellular traps. *Cell. Microbiol.* 9(5), 1162–1171.
- Weinberger, D. M., Dagan, R., Givon-Lavi, N., Regev-Yochay, G., Malley, R. & Lipsitch, M. (2008). Epidemiologic evidence for serotype-specific acquired immunity to pneumococcal carriage. *J. Infect. Dis.* 197(11), 1511–1518.
- Weinberger, D. M., Harboe, Z. B., Flasche, S., Scott, J. A. & Lipsitch, M. (2011). Prediction of serotypes causing invasive pneumococcal disease in unvaccinated and vaccinated populations. *Epidemiology*, 22(2), 199–207.
- Weinberger, D. M., Malley, R. & Lipsitch, M. (2011). Serotype replacement in disease after pneumococcal vaccination. *Lancet*, 378(9807), 1962–1973.
- Weinberger, D. M., Trzciński, K., Lu, Y.-J., Bogaert, D., Brandes, A., Galagan, J., ... Lipsitch, M. (2009). Pneumococcal capsular polysaccharide structure predicts serotype prevalence. *PLoS Pathog.* 5(6), e1000476.
- Weinert, L. a., Chaudhuri, R. R., Wang, J., Peters, S. E., Corander, J., Jombart, T., ... Terra, V. (2015). Genomic signatures of human and animal disease in the zoonotic pathogen streptococcus suis. *Nat. Commun.* 6, 6740.
- Weisfelt, M., van de Beek, D., Spanjaard, L., Reitsma, J. B. & de Gans, J. (2006). Clinical features, complications, and outcome in adults with pneumococcal meningitis: A prospective case series. *Lancet Neurol.* 5(2), 123–129.
- Willer, C. J., Li, Y. & Abecasis, G. R. (2010). METAL: Fast and efficient meta-analysis of genomewide association scans. *Bioinformatics*, 26(17), 2190–2191.
- Wilson, D. J., Gabriel, E., Leatherbarrow, A. J. H., Cheesbrough, J., Gee, S., Bolton, E., ... Fearnhead, P. (2009). Rapid evolution and the importance of recombination to the gastroenteric pathogen campylobacter jejuni. *Mol. Biol. Evol.* 26(2), 385–397.
- Winantea, J., Hoang, M. N., Ohlraun, S., Rietschel, M., Cichon, S., Propping, P., ... Freudenberg-Hua, Y. (2006). A summary statistic approach to sequence variation in noncoding regions of six schizophrenia-associated gene loci. *Eur. J. Hum. Genet.* 14(9), 1037–1043.
- Winkler, F., Kastenbauer, S., Yousry, T. A., Maerz, U. & Pfister, H.-W. (2002). Discrepancies between brain CT imaging and severely raised intracranial pressure proven by ventriculostomy in adults with pneumococcal meningitis. *J. Neurol.* 249(9), 1292–1297.
- Wise, A. L., Gyi, L. & Manolio, T. A. (2013). Exclusion: Toward integrating the X chromosome in genome-wide association analyses. *Am. J. Hum. Genet.* 92(5), 643–647.
- Woehrl, B., Brouwer, M. C., Murr, C., Heckenberg, S. G. B., Baas, F., Pfister, H. W., ... Van De Beek, D. (2011). Complement component 5 contributes to poor disease outcome in humans and mice with pneumococcal meningitis. *J. Clin. Invest.* 121(10), 3943–3953.

- Wood, D. E. & Salzberg, S. L. (2014). Kraken: Ultrafast metagenomic sequence classification using exact alignments. *Genome Biol.* 15(3), R46.
- Wörmann, M. E., Horien, C. L., Bennett, J. S., Jolley, K. a., Maiden, M., Tang, C. M., ... Exley, R. M. (2014). Sequence, distribution and chromosomal context of class I and class II pilin genes of neisseria meningitidis identified in whole genome sequences. *BMC Genomics*, 15, 253.
- Wright, S. (1920). The relative importance of heredity and environment in determining the piebald pattern of Guinea-Pigs. *Proceedings of the National Academy of Sciences*, 6(6), 320–332.
- Wu, M. C., Lee, S., Cai, T., Li, Y., Boehnke, M. & Lin, X. (2011). Rare-variant association testing for sequencing data with the sequence kernel association test. *Am. J. Hum. Genet.* 89(1), 82–93.
- Wyllie, A. L., Chu, M. L. J. N., Schellens, M. H. B., van Engelsdorp Gastelaars, J., Jansen, M. D., van der Ende, A., ... Trzciński, K. (2014). Streptococcus pneumoniae in saliva of dutch primary school children. *PLoS One*, 9(7), e102045.
- Wyllie, A. L., Wijmenga-Monsuur, A. J., van Houten, M. A., Bosch, A. A. T. M., Groot, J. A., van Engelsdorp Gastelaars, J., ... Trzciński, K. (2016). Molecular surveillance of nasopharyngeal carriage of streptococcus pneumoniae in children vaccinated with conjugated polysaccharide pneumococcal vaccines. *Sci. Rep.* 6, 23809.
- Yang, J., Benyamin, B., McEvoy, B. P., Gordon, S., Henders, A. K., Nyholt, D. R., ... Visscher, P. M. (2010). Common SNPs explain a large proportion of the heritability for human height. *Nat. Genet.* 42(7), 565–569.
- Yang, J., Lee, S. H., Goddard, M. E. & Visscher, P. M. (2011). GCTA: A tool for genome-wide complex trait analysis. *Am. J. Hum. Genet.* 88(1), 76–82.
- Yang, J., Manolio, T. A., Pasquale, L. R., Boerwinkle, E., Caporaso, N., Cunningham, J. M., ... Visscher, P. M. (2011). Genome partitioning of genetic variation for complex traits using common SNPs. *Nat. Genet.* 43(6), 519–525.
- Yang, L., Jelsbak, L., Marvig, R. L., Damkiær, S., Workman, C. T., Rau, M. H., ... Molin, S. (2011). Evolutionary dynamics of bacteria in a human host environment. *Proc. Natl. Acad. Sci. U. S. A.* 108(18), 7481–7486.
- Yang, Z. [Zhirong], Corander, J. & Oja, E. (2016). Low-Rank doubly stochastic matrix decomposition for cluster analysis. *J. Mach. Learn. Res.* 17(187), 1–25.
- Yang, Z. [Ziheng]. (2006). *Computational molecular evolution*. OUP Oxford.
- Yesilkaya, H., Spissu, F., Carvalho, S. M., Terra, V. S., Homer, K. A., Benisty, R., ... Andrew, P. W. (2009). Pyruvate formate lyase is required for pneumococcal fermentative metabolism and virulence. *Infect. Immun.* 77(12), 5418–5427.
- Yother, J. (2011). Capsules of streptococcus pneumoniae and other bacteria: Paradigms for polysaccharide biosynthesis and regulation. *Annu. Rev. Microbiol.* 65, 563–581.

- Young, B. C., Golubchik, T., Batty, E. M., Fung, R., Larner-Svensson, H., Votintseva, A. A., . . . Wilson, D. J. (2012). Evolutionary dynamics of staphylococcus aureus during progression from carriage to disease. *Proceedings of the National Academy of Sciences*, *109*(12), 4550–4555.
- Zafar, M. A., Wang, Y., Hamaguchi, S. & Weiser, J. N. (2017). Host-to-Host transmission of streptococcus pneumoniae is driven by its inflammatory toxin, pneumolysin. *Cell Host Microbe*, *21*(1), 73–83.
- Zaharia, M., Bolosky, W. J., Curtis, K., Fox, A., Patterson, D. A., Shenker, S., . . . Sittler, T. (2011). Faster and more accurate sequence alignment with SNAP. *CoRR*, *abs/1111.5*, 1–10.
- Zerbino, D. R. & Birney, E. (2008). Velvet: Algorithms for de novo short read assembly using de bruijn graphs. *Genome Res.* *18*(5), 821–829.
- Zhang, F.-R., Huang, W., Chen, S.-M., Sun, L.-D., Liu, H., Li, Y., . . . Liu, J.-J. (2009). Genomewide association study of leprosy. *N. Engl. J. Med.* *361*(27), 2609–2618.
- Zhou, X. & Stephens, M. (2012). Genome-wide efficient mixed-model analysis for association studies. *Nat. Genet.* *44*(7), 821–824.
- Zimin, A. V., Marçais, G., Puiu, D., Roberts, M., Salzberg, S. L. & Yorke, J. a. (2013). The MaSuRCA genome assembler. *Bioinformatics*, *29*(21), 2669–2677.