

Section 2: Single locus to multi-locus ‘Genes to Genomes’

Molecular Approaches to Clinical Microbiology in Africa 2024

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OXFORD

Learning Outcomes

After this lecture you should understand:

1. The nature and extent of bacterial diversity.
2. How sequence data illuminate bacterial diversity.
3. The variety of bacterial population structures and the implications of horizontal gene transfer (HGT).
4. Practical implications of molecular epidemiology and population biology.

Questions in clinical microbiology

evolution

Centuries+

emergence

decades

years

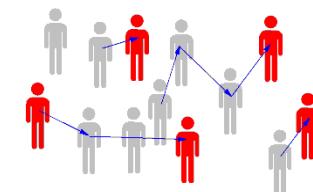
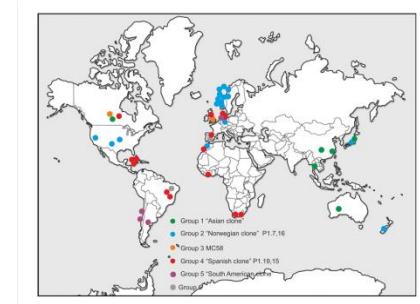
epidemiology

months

weeks

diagnosis

hours



High

Low

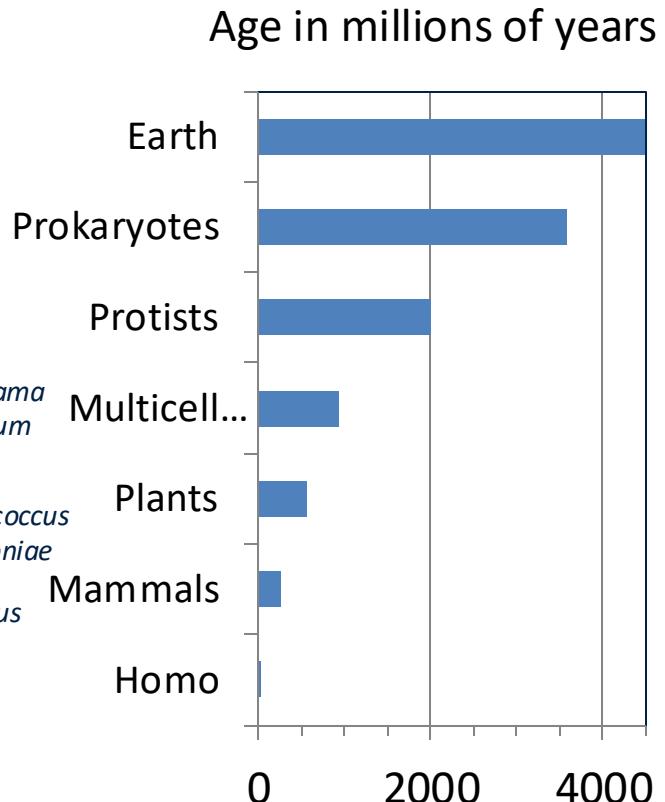
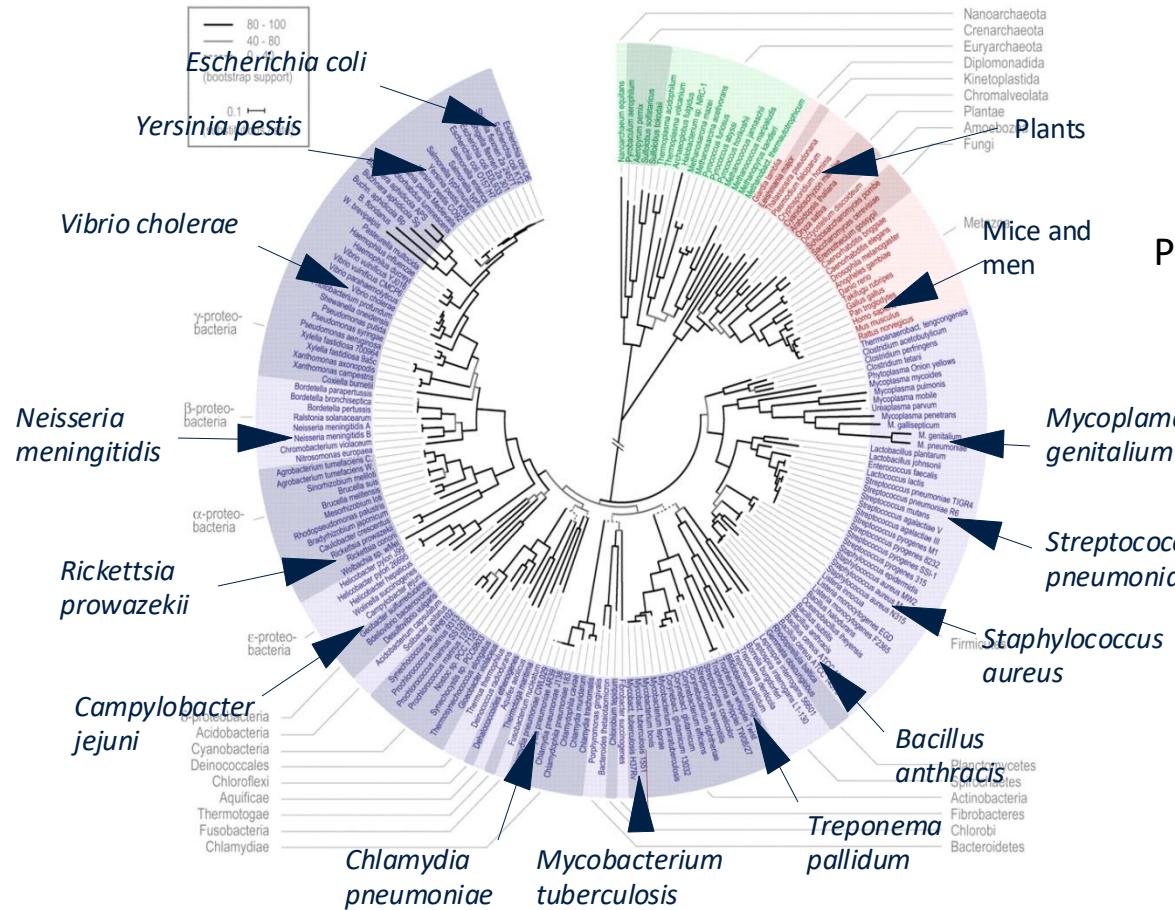
Relative amount of genetic change

Low

High

Relative discrimination required

The scale of the problem: planet of the bacteria



Stephen Jay Gould, "Planet of the Bacteria," Washington Post Horizon, 1996, 119 (344)

Ciccarelli, F. D., Doerks, T., von Mering, C., Creevey, C. J., Snel, B. & Bork, P. (2006). Toward automatic reconstruction of a highly resolved tree of life. *Science* 311, 1283-1287.

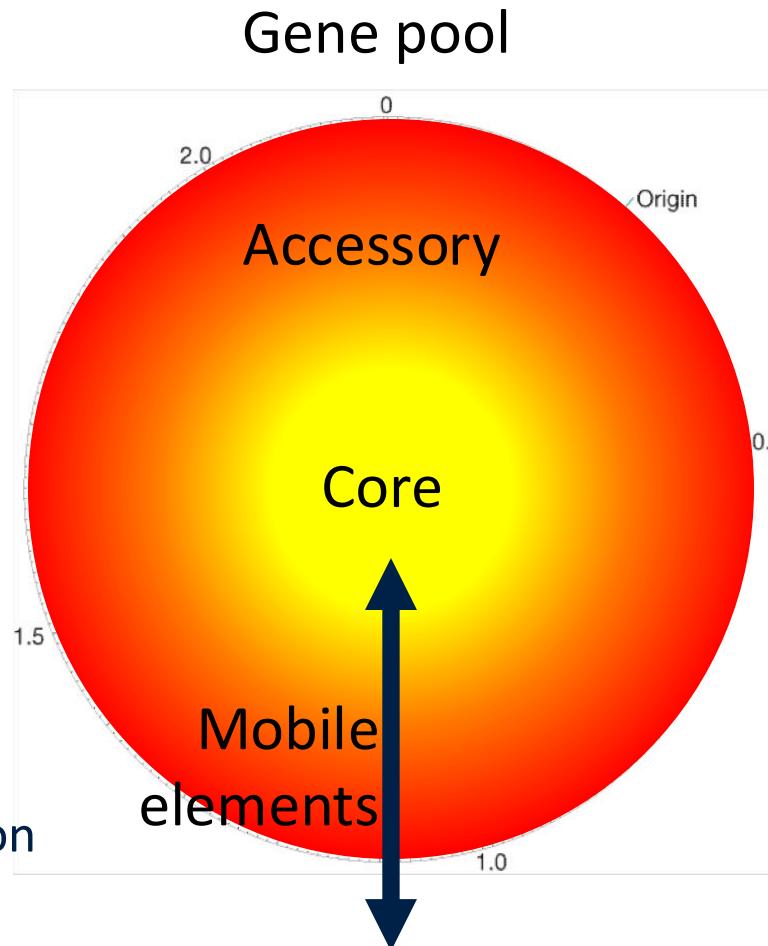
The scale of the problem: bacterial genome diversity

Core genome:

e.g. DNA replication, ribosomes, cell envelope, key metabolic pathways.

Parasitic elements (phages plasmids)

e.g. toxins, restriction/modification systems.



Accessory genome:

e.g. alternative metabolic pathways, transport systems.

Tettelin, H., Riley, D., Cattuto, C. & Medini, D. (2008). Comparative genomics: the bacterial pan-genome. *Current Opinion in Microbiology* 11, 472-477.

Gene pool:

e.g. antibiotic resistance, degradative metabolism.

Genetic elements may be subject to **stabilising (negative)** or **diversifying (positive)** selection or be **neutral** (rare in most bacteria).

Implications of bacterial diversity for clinical microbiology

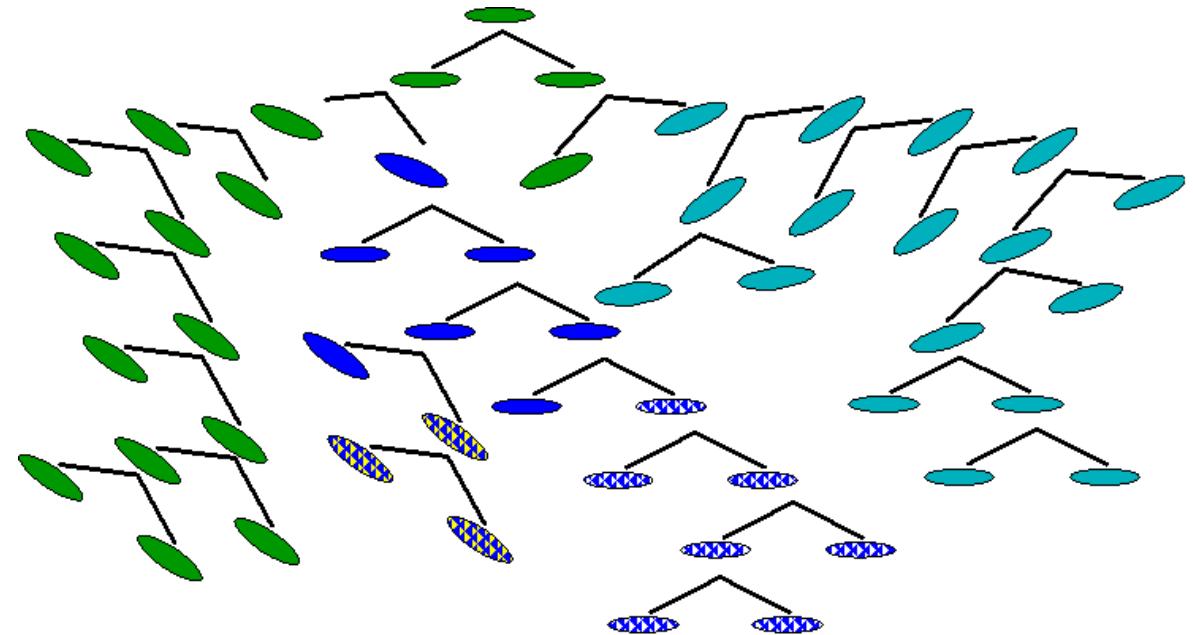
- The information required by practitioners includes:
 - what organism is causing disease;
 - what are its characteristics (antimicrobial resistance, vaccine antigens);
 - how is it related to other organisms (epidemiology, outbreak control).
- Determining this from sequence data depends on:
 - the degree of variation present;
 - how the variation is structured.
- This varies widely among bacteria, which determines:
 - what data are required;
 - how much data are required; and,
 - how they are analysed.

Patterns in sequence variation

a primer on bacterial population biology

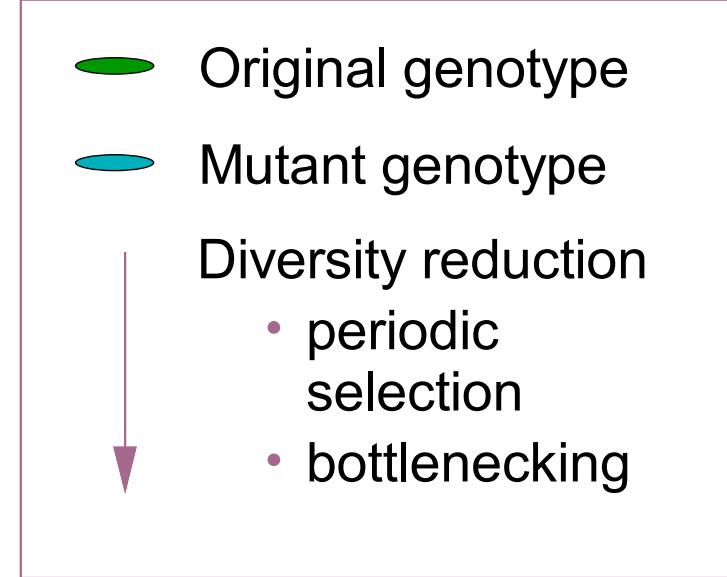
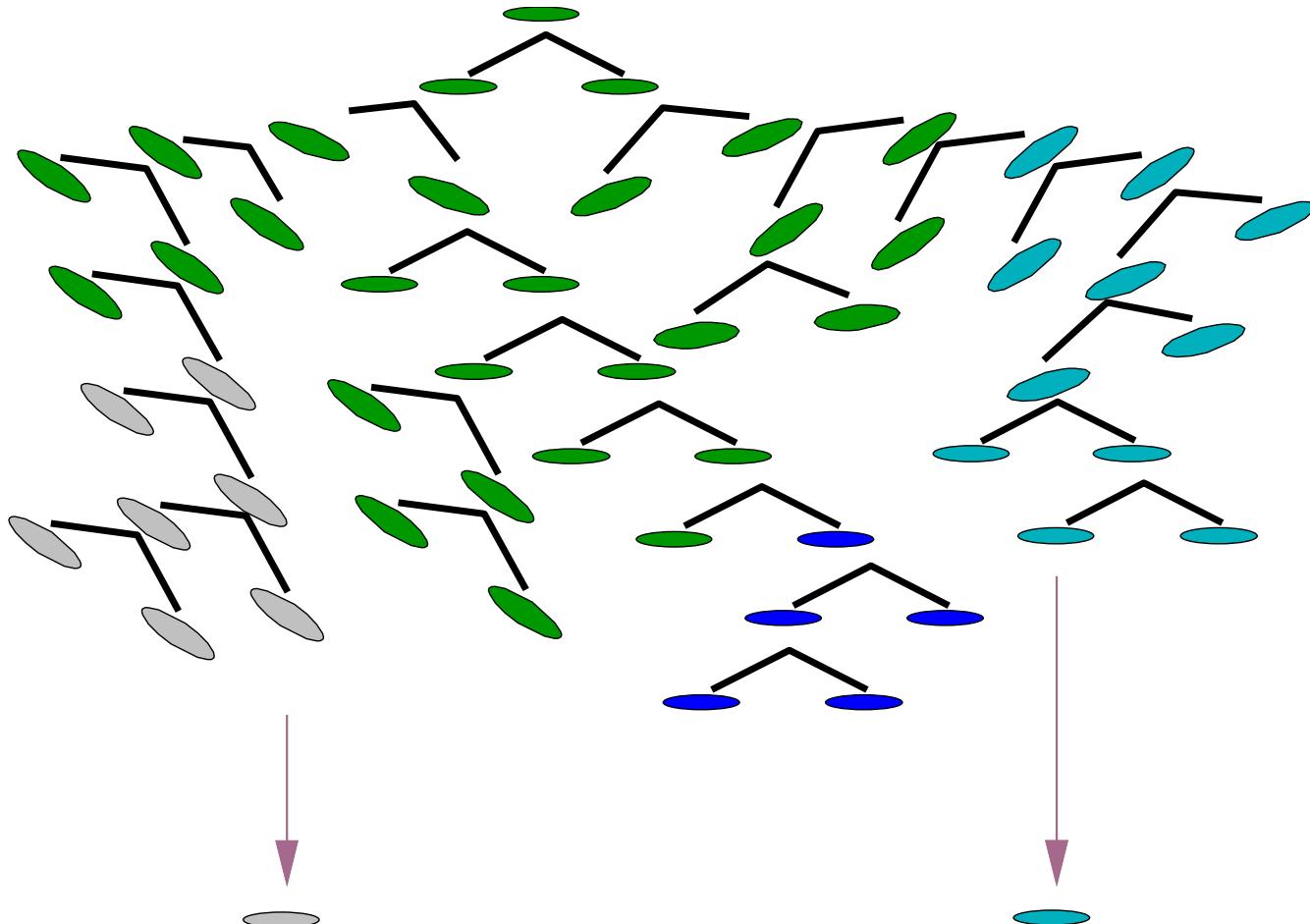
Ideas about bacterial populations are dominated by the facts that bacteria:

- are asexual;
- reproduce by binary fission, with each ‘mother’ cell giving rise to two identical ‘daughter’ cells (**clones**);
- accumulate genetic change by ‘vertical’ inheritance.



Gupta, S. & Maiden, M.C.J. (2001). Exploring the evolution of diversity in pathogen populations. *Trends in Microbiology* 9, 181-192.

The clonal population model: asexuality with diversity reduction



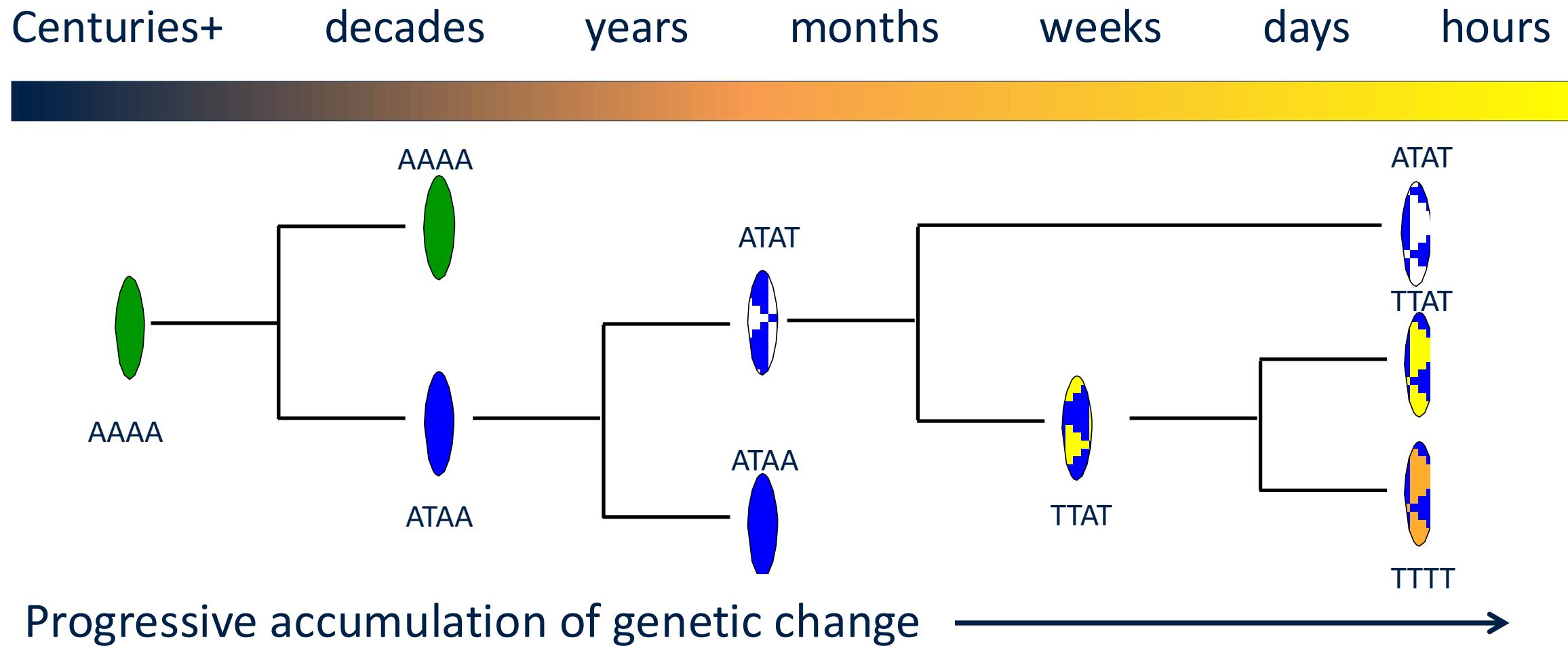
Levin BR. 1981. Periodic selection, infectious gene exchange and the genetic structure of *E. coli* populations. *Genetics* 99(1):1-23.

Within this model, Bacterial populations are (relatively) easy to understand.

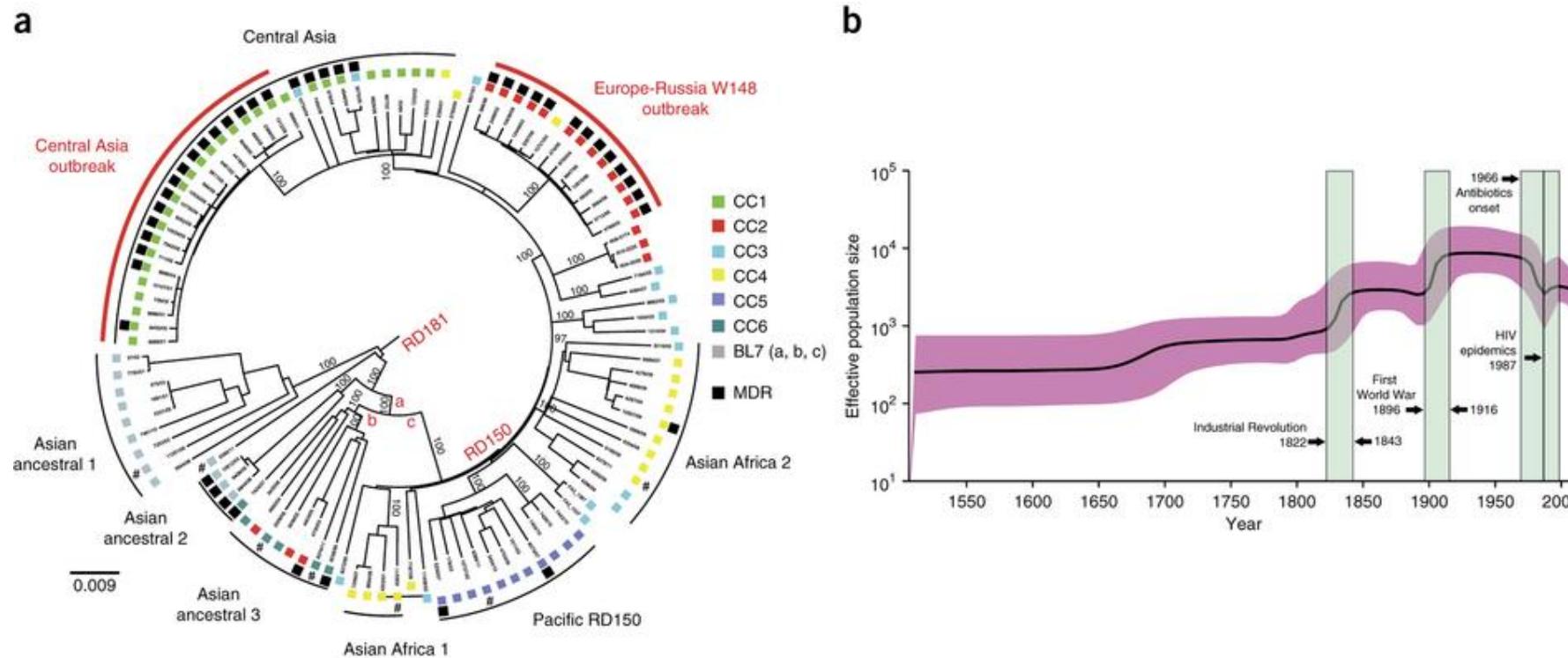
Selection pressures and impact on sequences

- **Diversifying (directional, positive) selection** – changes fitness phenotype
 - e.g. nonsynonymous mutations leading to antigenic diversity or antimicrobial resistance and mutations that change expression.
- **Stabilising selection (purifying, negative) selection** – retains phenotype and fitness
 - the gene or its expression is unchanged e.g. ‘housekeeping genes’.
- **Neutral variation** – variation that does not impact on fitness phenotype
 - synonymous changes may or may not be neutral in any gene.

Molecular epidemiology made easy: clonality



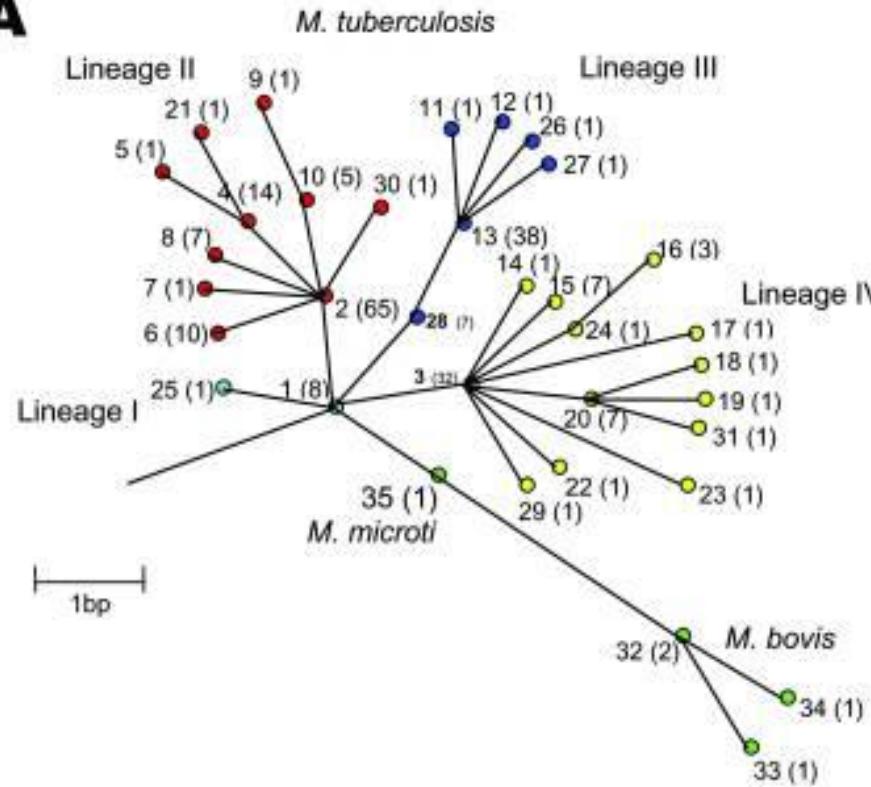
Mycobacterium tuberculosis is clonal: spread of the Beijing lineage



Merker, M., Blinet. Al. (2015). Evolutionary history and global spread of the *Mycobacterium tuberculosis* Beijing lineage. *Nat Genet* **47, 242-249.**

Mycobacterium tuberculosis lineages resolved by synonymous (silent) substitutions

A



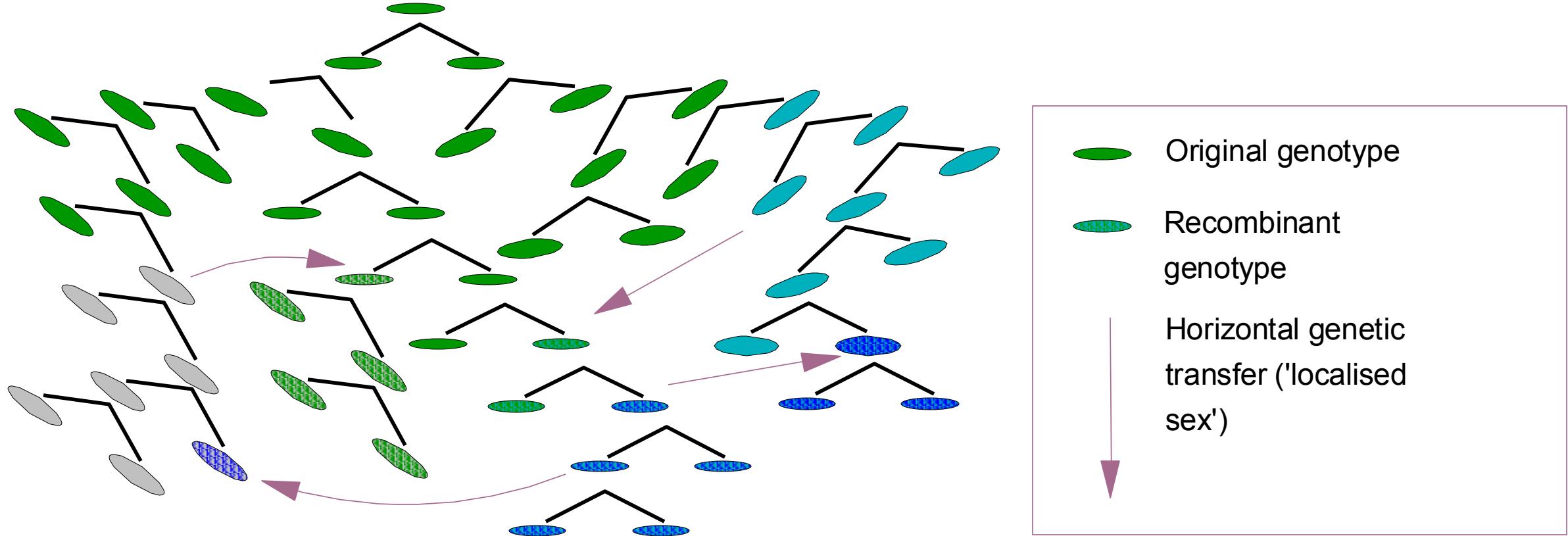
Gene	oxyR										ahpC										katG										rpoB									
	Nucleotide position		37	204	263	285	18	480	87	399	555	609	891	942	1563	1599	1821	6	195	201	300	318	327	357	702	1701	2646	3243												
	Codon number		6	160	29	133	185	203	297	314	521	533	607	2	65	67	100	106	109	119	194	567	882	1081																
Amino acid		Ile	Glu	Pro	Asn	Phe	Thr	Gly	Thr	Leu	Pro	Glu	Arg	Ser	Ser	Thr	Ser	Asp	Val	Val	Glu	Gly	Ala																	
Lineage I	SST 1	C	A	C	G	T	G	C	C	C	C	C	G	G	G	G	C	G	C	C	C	G	C	C	C	G	T	C												
	25										
Lineage II	2										
	4										
	5										
	21										
	10										
	9										
	6										
Lineage III	28										
	13										
	26										
	27										
Lineage IV	3	T										
	20	T										
	18	T										
	19	T										
	31	T										
	24	T										
	16	T										
	15	T	C										
	17	T										
<i>M. bovis</i>	32	A										
	33	A										
	34	A										
<i>M. microti</i>	35										

Baker, L., Brown, T., Maiden, M. C. & Drobniewski, F. (2004). Silent nucleotide polymorphisms and a phylogeny for *Mycobacterium tuberculosis*. *Emerging Infectious Diseases*. **10**, 1568-1577.

What is a bacterial species?

- In animals, and particularly mammals, species are defined by the ability to produce fertile offspring,
 - this does not, however, work well for other organisms.
- The concept of bacterial species is surprisingly controversial,
 - in terms of whether they exist, what they are, and how they are defined.
- From a clinical point of view, pragmatic definitions are important,
 - e.g. *Yersina pestis* and *Bacillus anthracis* are both genetically very close to their relatives, yet sufficiently clinically important and biologically distinct to warrant species designations.
- Pragmatically, bacterial species comprise organisms that have distinct phenotypes (e.g. causing plague or anthrax) and genotypes,
 - usually they are maintained by limitations of genetic exchange with close relatives.

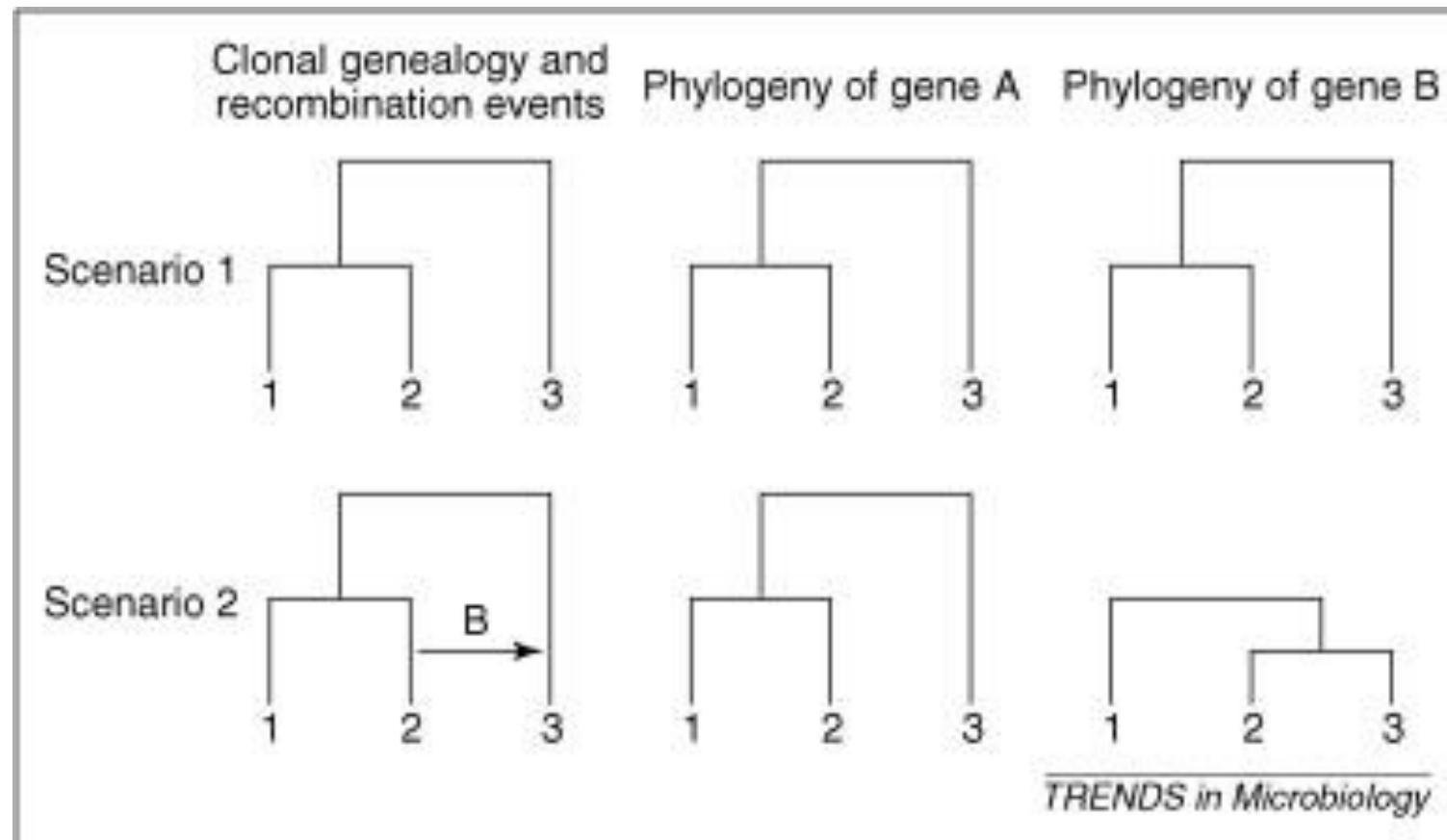
Impact of Horizontal genetic exchange (HGT) on bacterial population structure



HGT disrupts clonal structure, breaking down tree-like phylogeny, linkage disequilibrium and congruence.

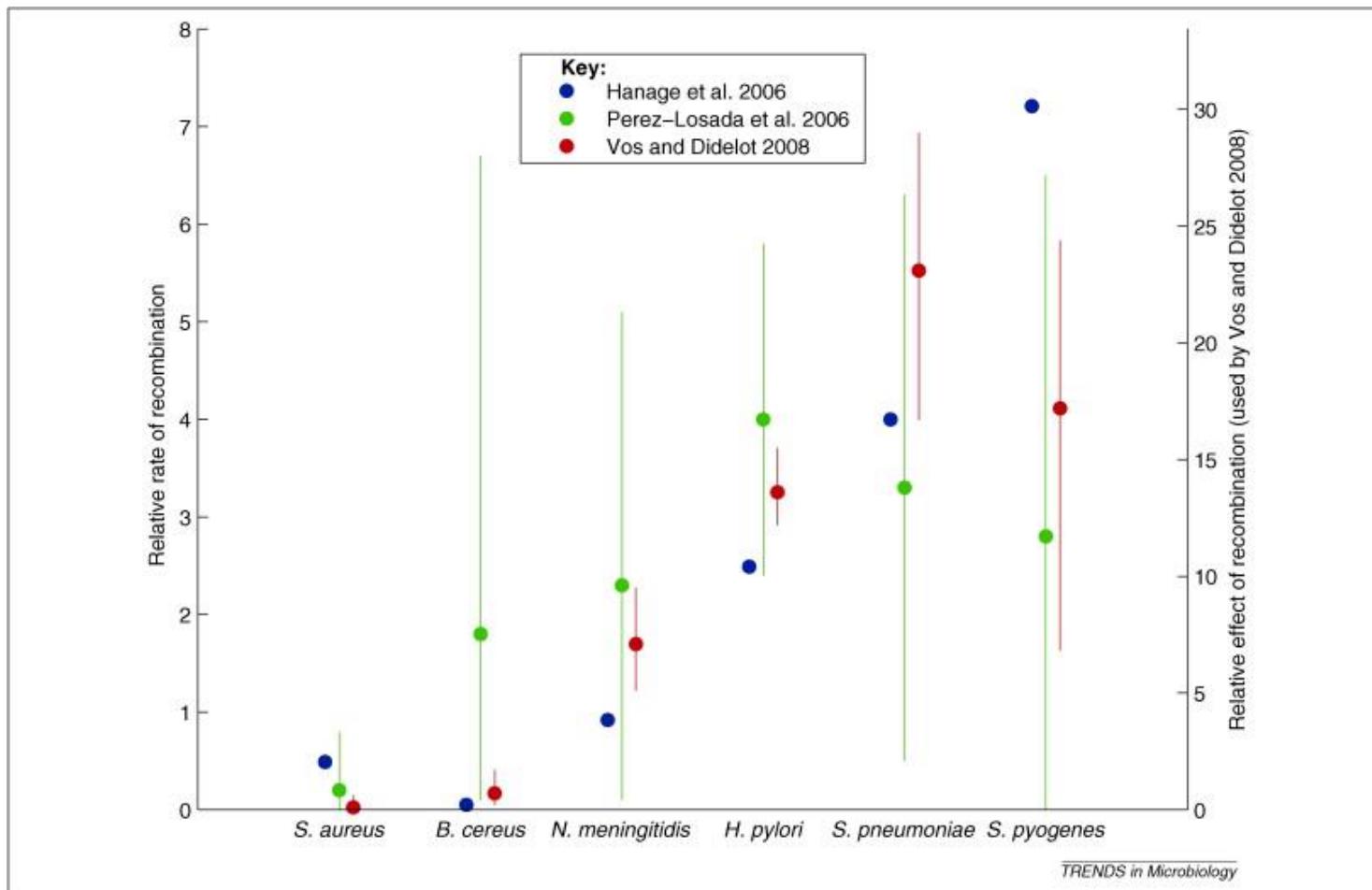
Maynard Smith J, Dowson CG, Spratt BG. (1991). Localized sex in bacteria. *Nature* **349, 29-31.**

Recombination and phylogeny



Didelot, X. & Maiden, M. C. (2010). Impact of recombination on bacterial evolution. *Trends in Microbiology* 18, 315-322.

Varying impact of recombination



Didelot, X. & Maiden, M. C. (2010). Impact of recombination on bacterial evolution. *Trends in Microbiology* 18, 315-322.

Clonal and non-clonal population structures

Clonal

- Linkage disequilibrium
 - non-random allele combinations.
- Tree-like phylogeny
 - a bifurcating tree accurately models descent.
- Congruence
 - the same phylogenetic signal is recorded throughout the genome.

Non-clonal

- Linkage equilibrium
 - random allele combinations.
- Net-like phylogeny
 - a bifurcating tree cannot model descent.
- Incongruence
 - different phylogenetic signals are recorded throughout the genome.

Dealing with partial HGT

HGT violates the assumptions of clonal evolution and can be accounted for in models of bacterial evolution by:

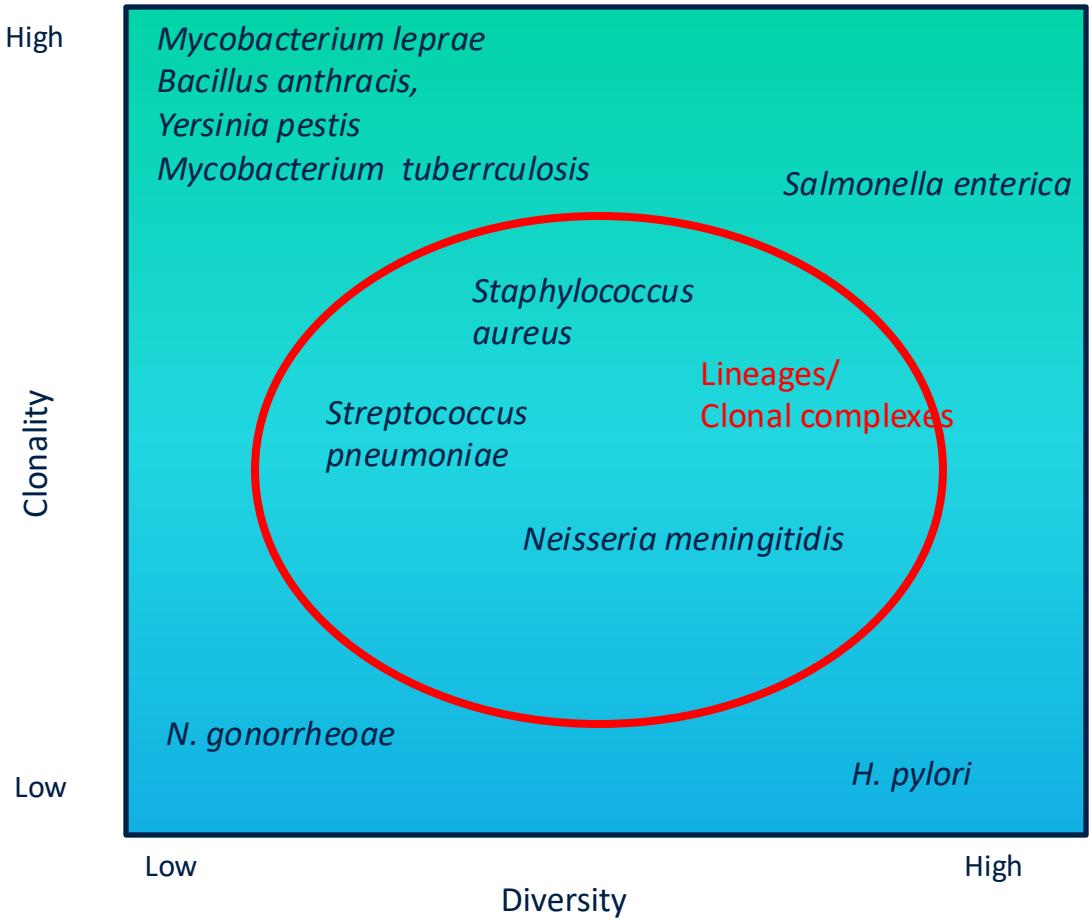
- Ignoring it, which only works if HGT is uncommon;
- Using loci and alleles as the unit of analysis (*e.g.* gene-by-gene MLST approaches);
- Identifying likely HGT and removing it (*e.g.* GUBBINS);
- Estimating relative contributions of recombination and mutation in evolutionary models (*e.g.* ClonalFrame ML).

Population structure and diversity

In conclusion:

- different levels of clonal signal are observed in different bacterial populations;
- this is a consequence of differing relative rates of recombination to mutation;
- however, other forces will also play a role.

Didelot, X. & Maiden, M. C. J. (2010).
Impact of recombination on bacterial evolution. *Trends Microbiol* 18, 315-322.

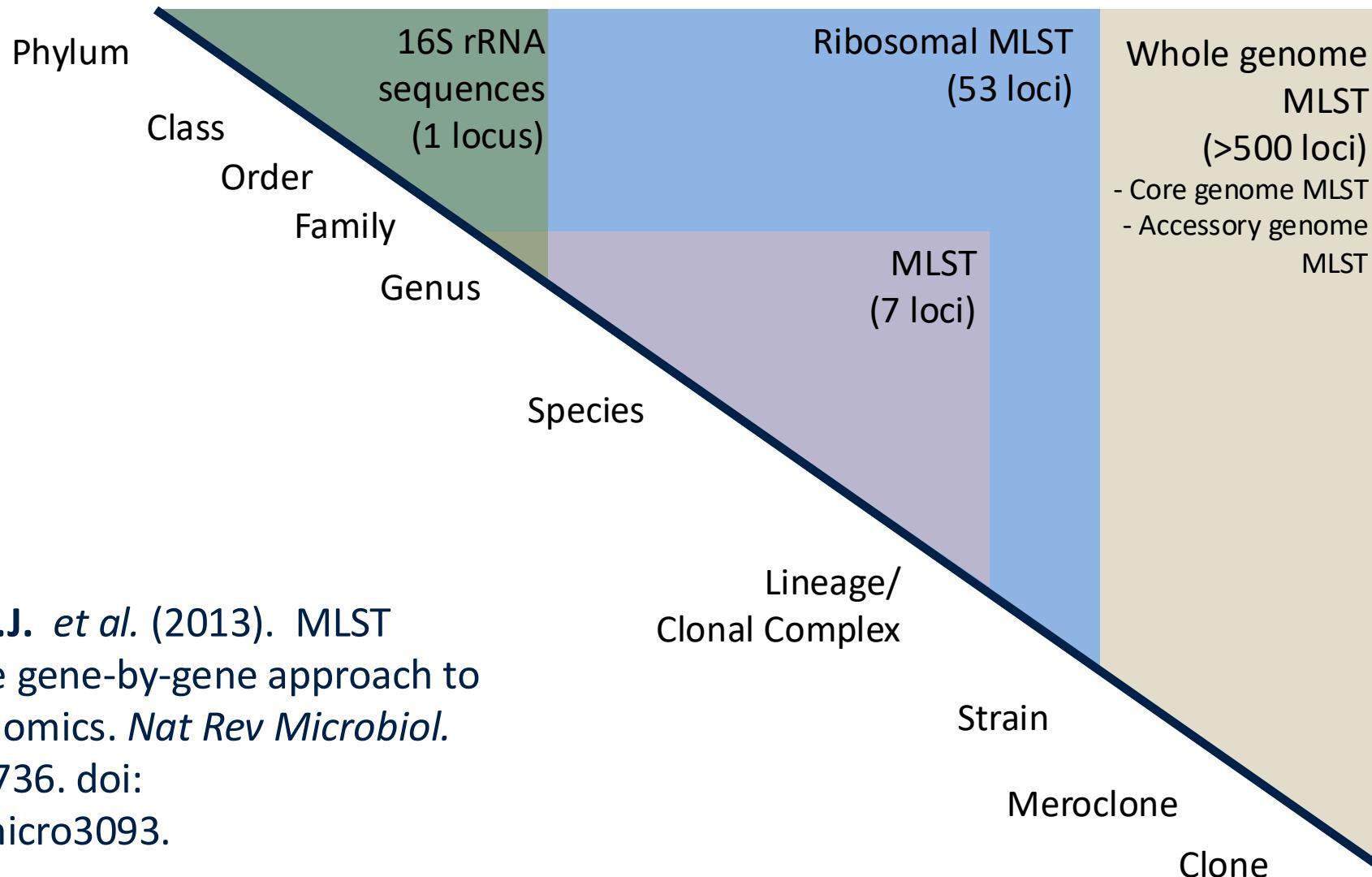


Summary

- Bacterial populations are extremely ancient,
 - bacterial diversity is almost unimaginably large.
- The bacterial population diversity has been shaped by selective forces,
 - positive (diversifying) selection, negative (stabilising) selection, neutrality.
- Extensive diversity is present within as well as among genomes,
 - HGT mobilises this diversity, as seen in the spread of AMR.
- Limitations in HGT enable species and distinct types to emerge,
 - the ratio of mutation to genetic transfer (recombination) affects population structure.

Within and among species diversity,
exemplified by the *Neisseria*

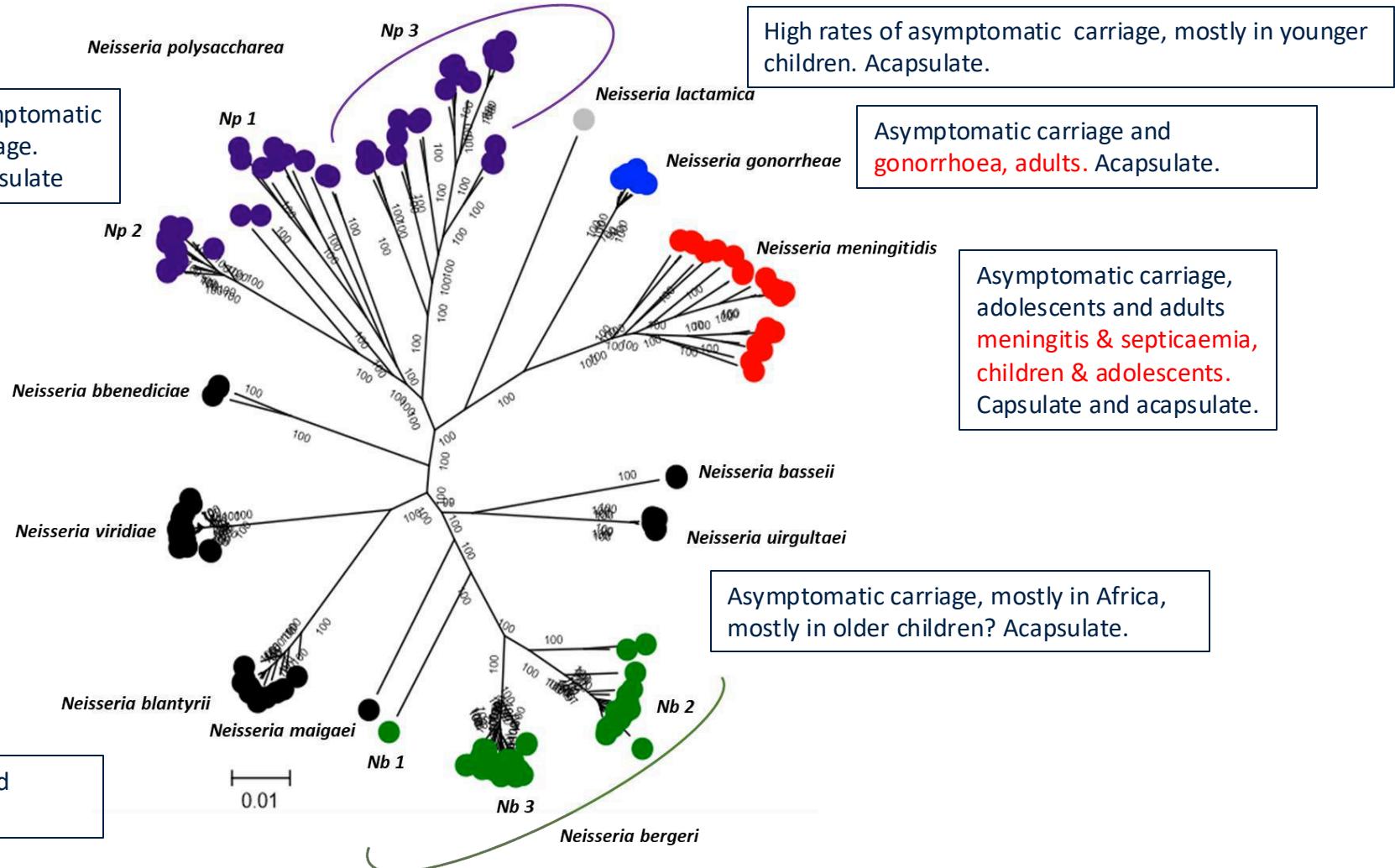
Sequence data and nomenclature



What is a species? Genus *Neisseria*, cgMLST 95% ANI threshold

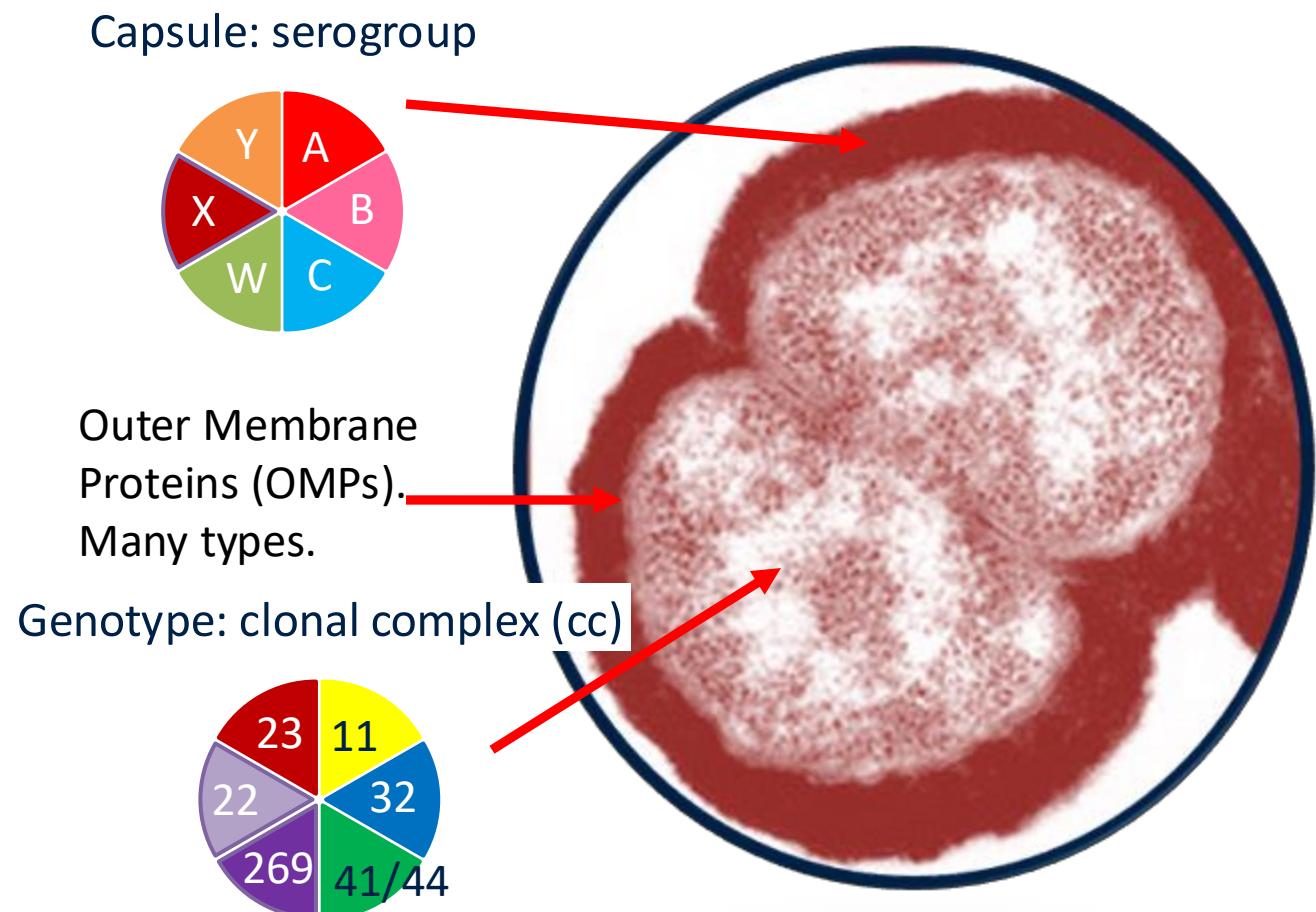
Diallo, K., MacLennan, J.,
Harrison, O.B., Msefula, C.
Sow, S.O., Daugla, D.M.,
Johnson, E., Trotter, C.,
MacLennan, C.A., Parkhill, J.,
Borrow, R., Greenwood, B.M.
and Maiden, M.C.J. (2019)
Genomic characterization of
novel *Neisseria* species
Scientific Reports, 9, 13742.

Other species are associated with dental and mucosal colonisation in animals and man.



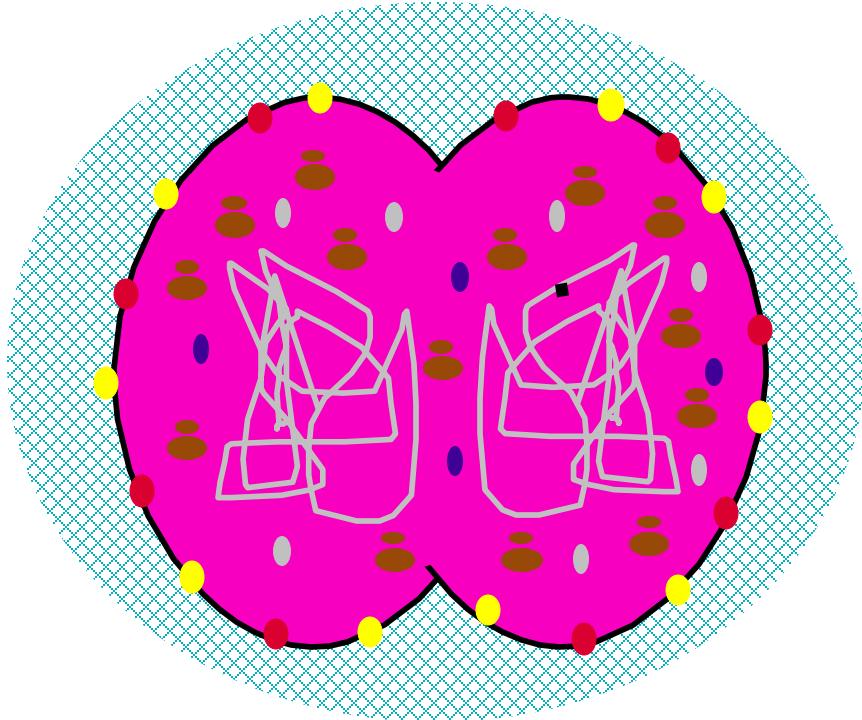
Within species diversity *Neisseria meningitidis*

- Meningococci are highly diverse antigenically and genetically,
 - this diversity is structured.
- 12 capsular serogroups,
 - 6 associated with invasive disease.
- Extensive evidence of HGT, but stable lineages are present,
 - these are associated with phenotypes, including invasive disease.



Ganesh, K., Allam, M., Wolter, N., Bratcher, H. B., Harrison, O. B., Lucidarme, J., Borrow, R., de Gouveia, L., Meiring, S., Birkhead, M., Maiden, M. C., von Gottberg, A. & du Plessis, M. (2017). Molecular characterization of invasive capsule null *Neisseria meningitidis* in South Africa. *BMC Microbiology* **17**, 40.

Case Study, assembling a ‘Strain type’ or ‘fine type’: *Neisseria meningitidis* characterisation

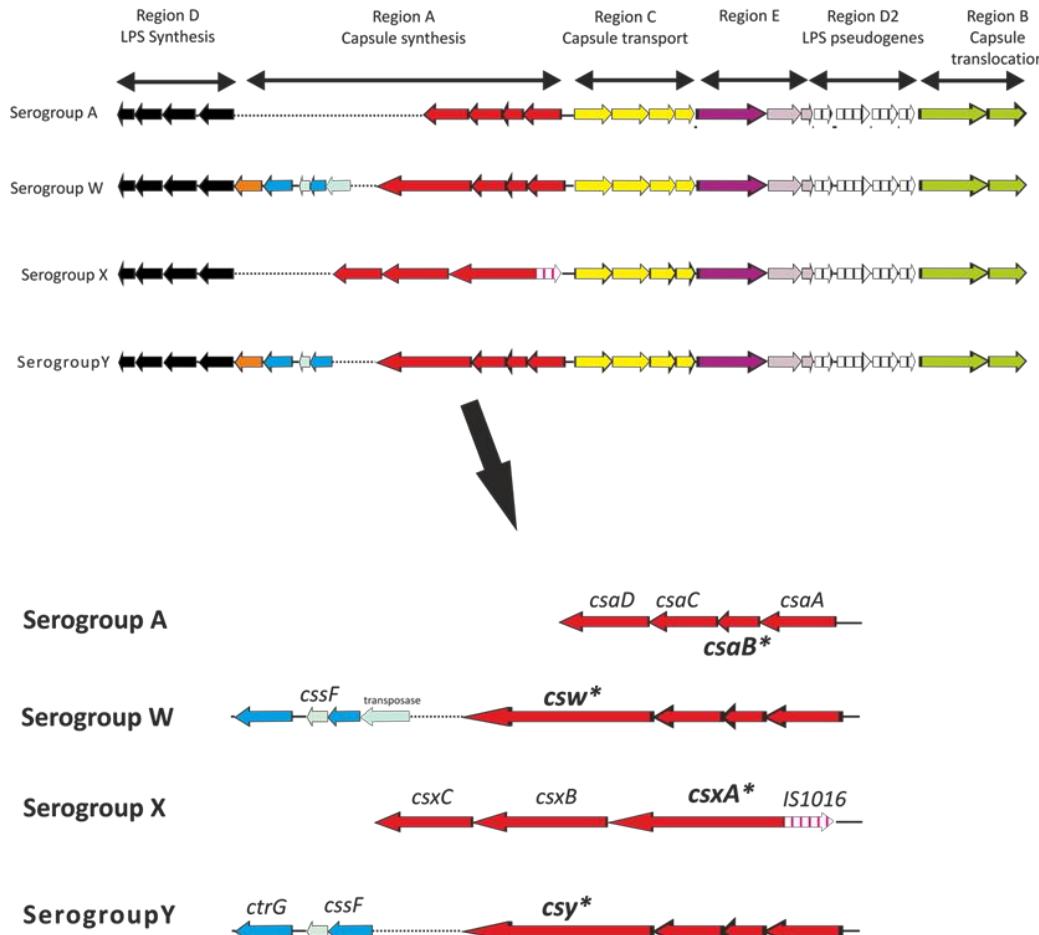


Component	Phenotypic	Genotypic
Capsule	Serogroup	<i>cps</i> region
OMPS	Serotype, Subtype, etc.	<i>porA</i> , <i>porB</i> , <i>fetA</i> , etc.
Housekeeping genes	MLEE	MLST
Ribosomes	MALDI-TOF	16s rRNA, rMLST

Neisseria meningitidis C: P1.21-15,16: F1-7: ST-10217 (cc10217)

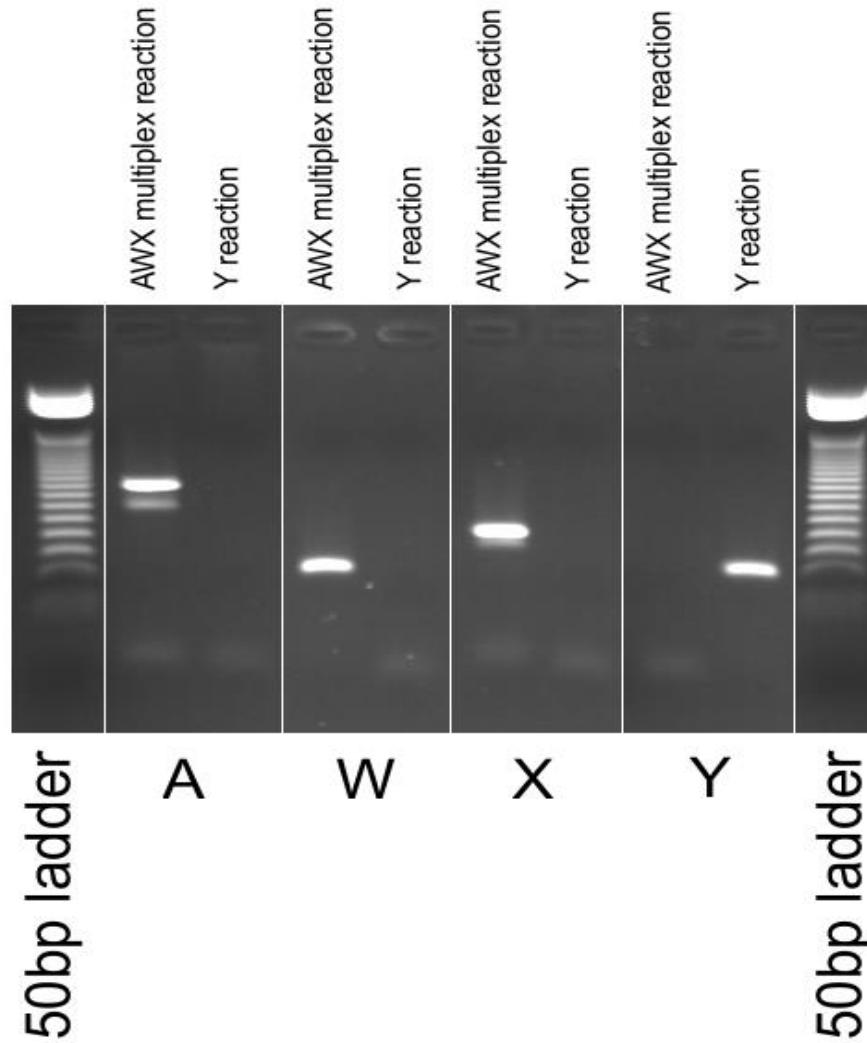
Jolley, K. A., Brehony, C. & Maiden, M. C. (2007). Molecular typing of meningococci: recommendations for target choice and nomenclature. *FEMS Microbiol Rev* **31**, 89-96.

Meningococcal genogrouping: characterising the *cps* region encoding the capsule (serogroup antigen)



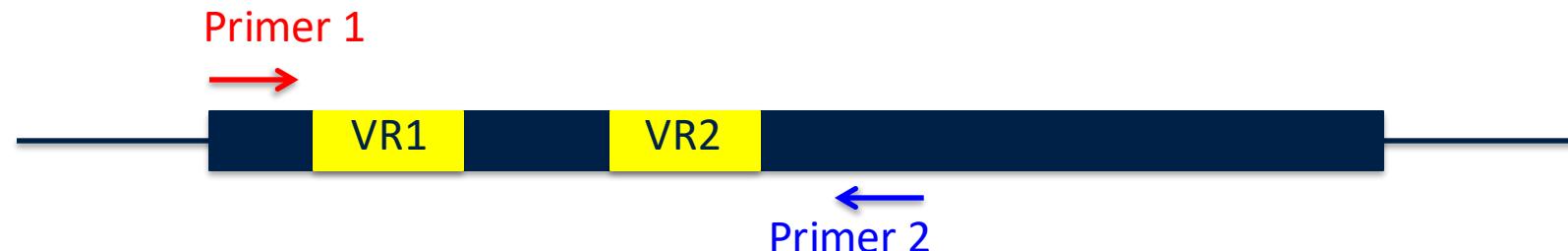
Harrison, O. B., Claus, H., Jiang, Y., Bennett, J. S., Bratcher, H. B., Jolley, K. A., Corton, C., Care, R., Poolman, J. T., Zollinger, W. D., Frasch, C. E., Stephens, D. S., Feavers, I., Frosch, M., Parkhill, J., Vogel, U., Quail, M. A., Bentley, S. D. & Maiden, M. C. J. (2013). Description and nomenclature of *Neisseria meningitidis* capsule locus. *Emerging Infectious Diseases* 19, 566-573.

Genogrouping: a PCR will do it

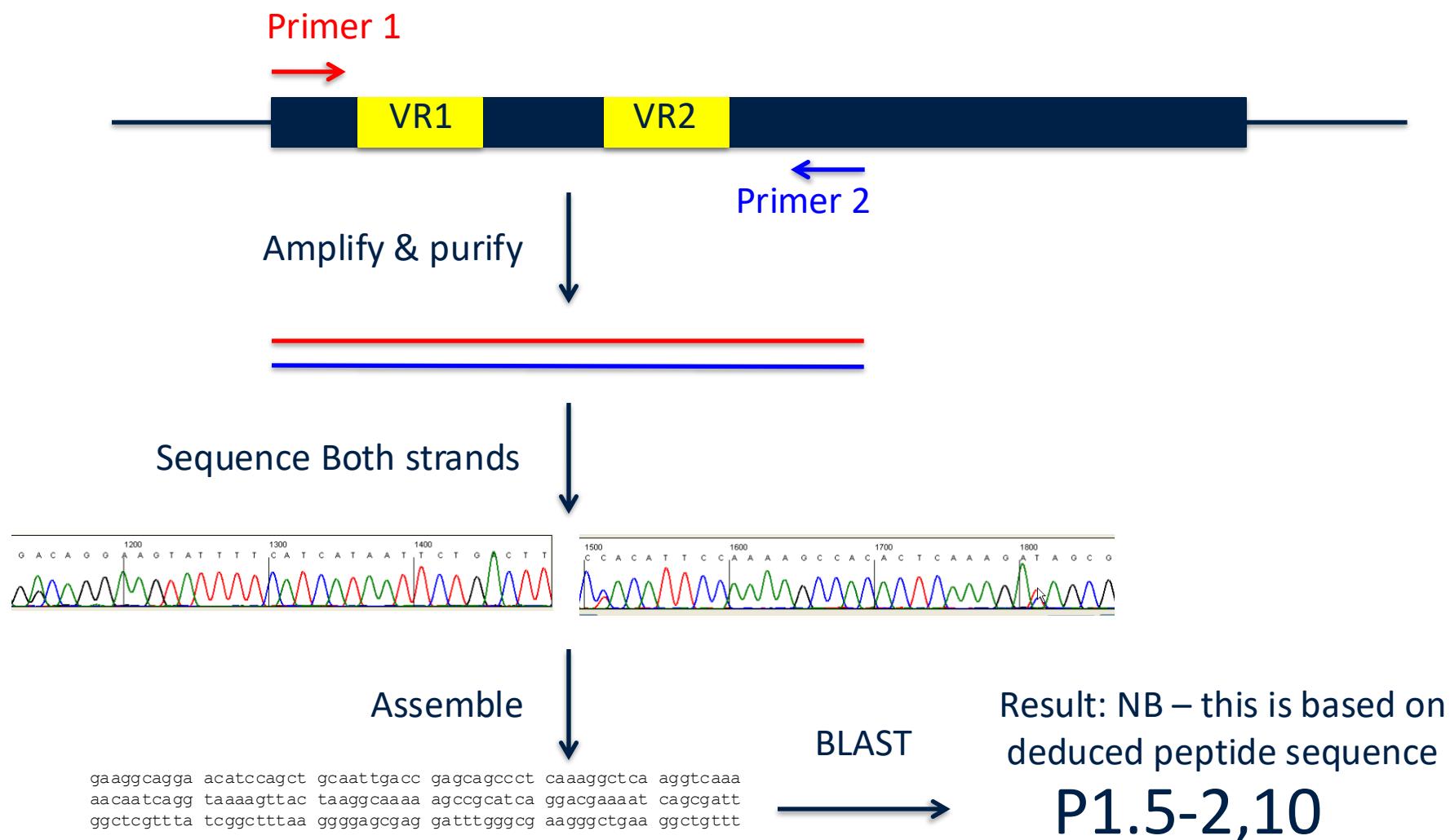


Meningococcal characterization: sequence-based subtyping

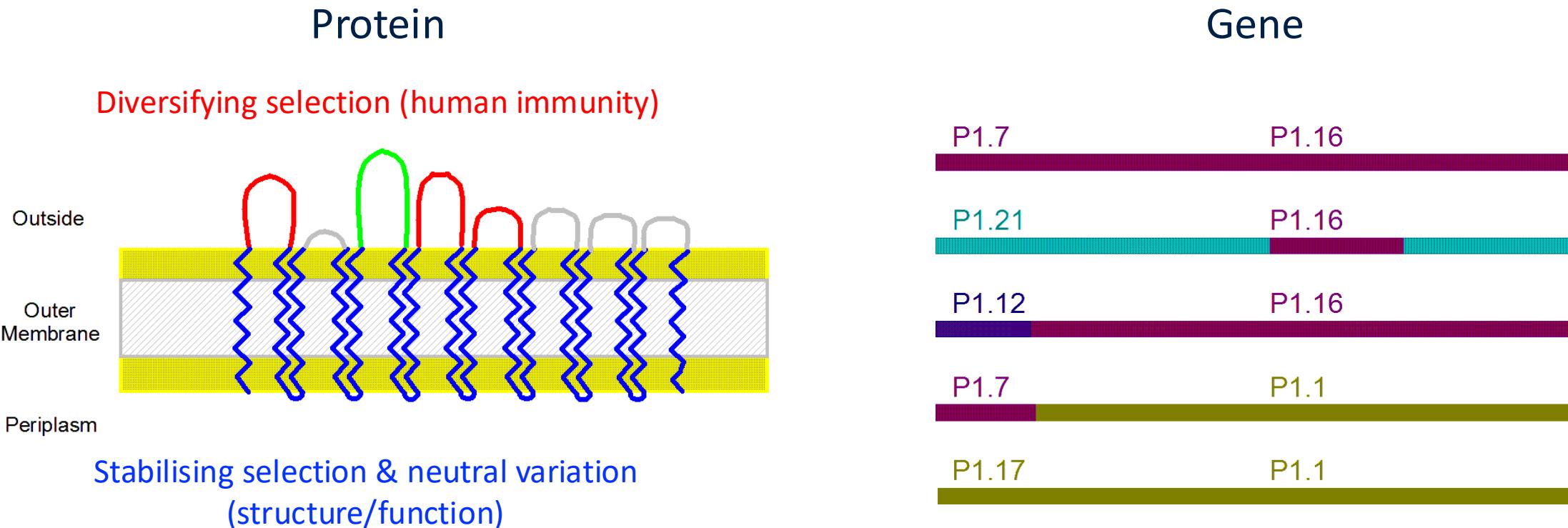
- The two most variable parts of the protein (VR1 and VR2) are close together,
 - one sequencing reaction can determine the parts of the gene encoding both of these.
- *porA* gene fragment sequencing therefore extracts a lot of information for the amount of sequencing performed.



Sequencing *porA* VR1 and VR2



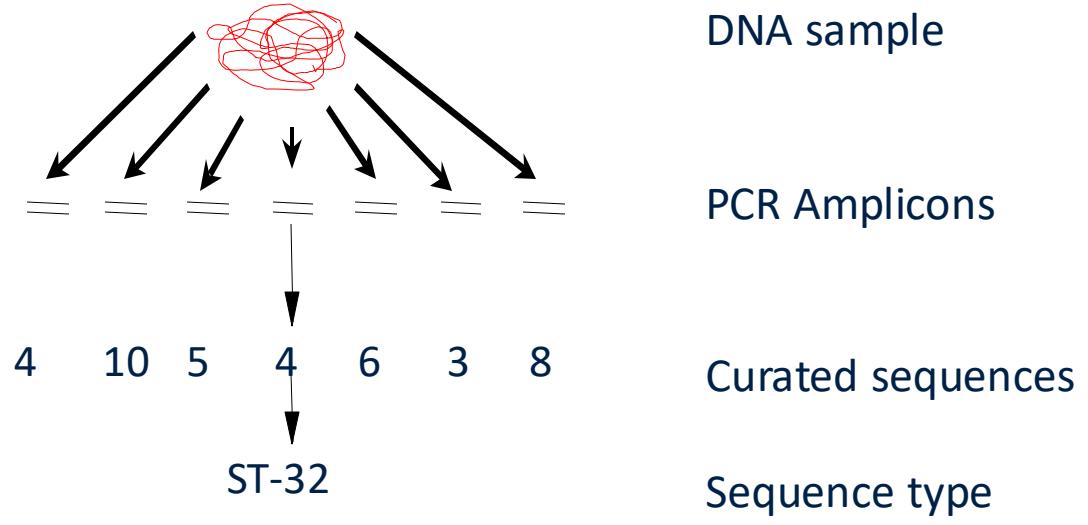
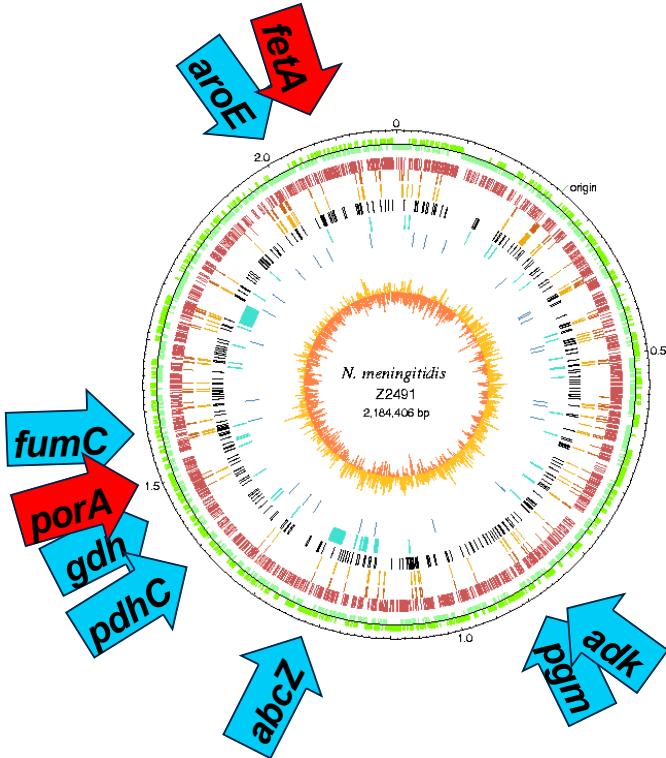
Meningococcal horizontal genetic transfer: mosaic *porA* genes



Maiden MCJ, Suker J, McKenna AJ, Bygraves JA, Feavers IM. Comparison of the class 1 outer membrane proteins of eight serological reference strains of *Neisseria meningitidis*. Mol. Microbiol. 1991;5:727-736.

Feavers IM, Heath AB, Bygraves JA, Maiden MC. Role of horizontal genetic exchange in the antigenic variation of the class 1 outer membrane protein of *Neisseria meningitidis*. Molecular Microbiology 1992;6:489-495.

PCR Sequence based typing: single locus and MLST



B: P1.7,16: F5-1: ST-32 (cc32)

Antigen type &
(fine type) Sequence type &
clonal complex

Maiden, MCJ, Bygraves, JA, Feil, E, Morelli, G, Russell, JE, Urwin, R, Zhang, Q, Zhou, J, Zurth, K, Caugant, DA, Feavers, IM, Achtman, M & Spratt, BG.
1998. Multilocus sequence typing: a portable approach to the identification of clones within populations of pathogenic microorganisms. Proc Natl Acad Sci USA 95, 3140-3145.

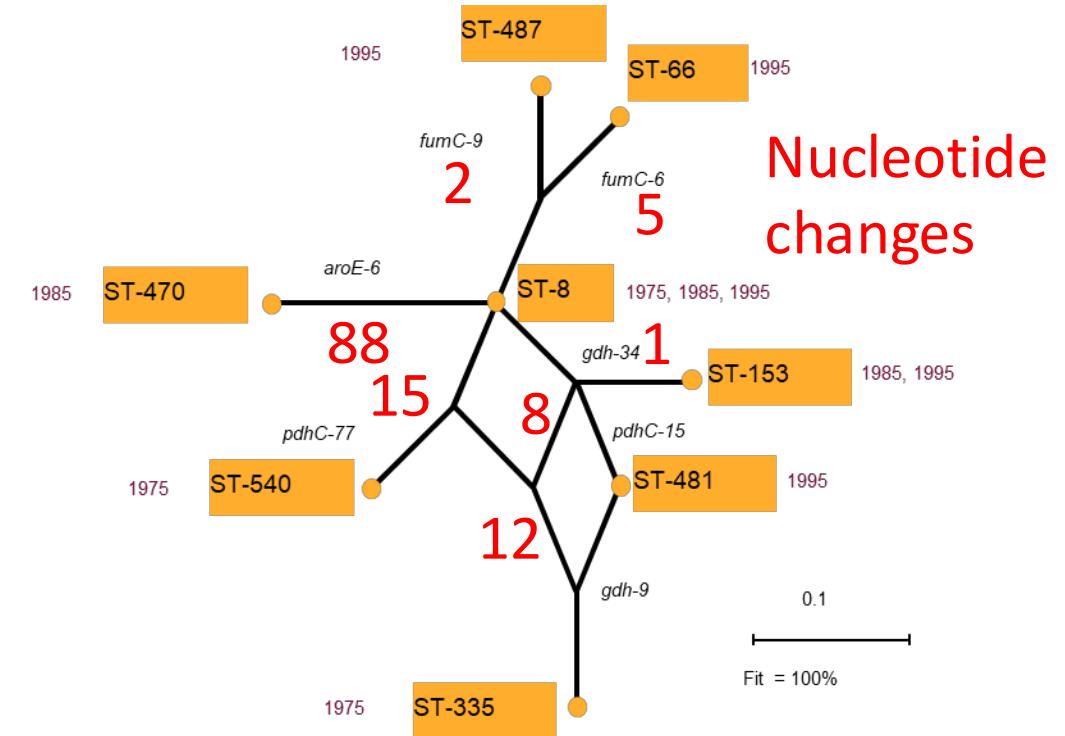
Maiden, MC. 2006. Multilocus Sequence Typing of Bacteria. Annu Rev Microbiol 60, 561-588.

Jolley KA, Brehony C, Maiden MC. 2007. Molecular typing of meningococci: recommendations for target choice and nomenclature. FEMS Microbiol Rev 31, 89-96.

MLST: allele-based analyses, sequence types (STs) and clonal complexes (ccs)

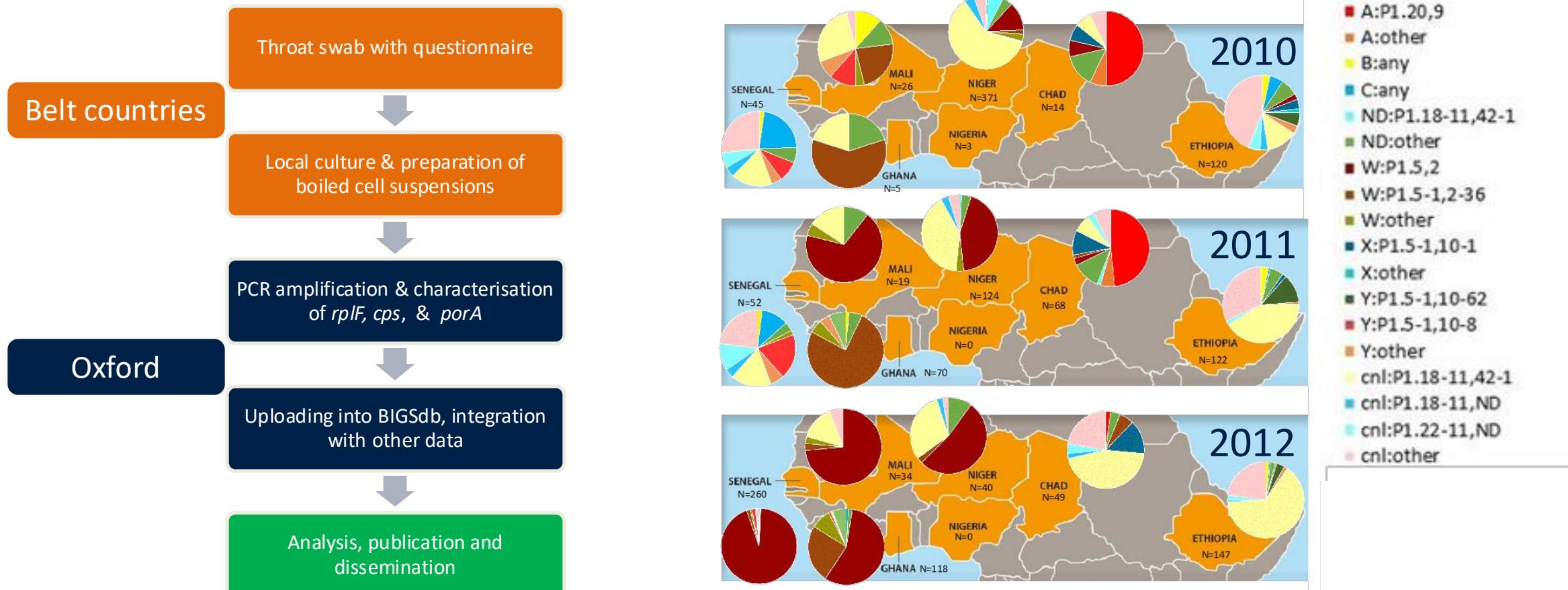
ST	<i>adk</i>	<i>abcZ</i>	<i>aroE</i>	<i>fumC</i>	<i>gdh</i>	<i>pdhc</i>	<i>pgm</i>
8	2	3	7	2	8	5	2
66	2	3	7	6	8	5	2
153	2	3	7	2	34	5	2
335	2	3	7	2	9	15	2
470	2	3	6	2	8	5	2
481	2	3	7	2	9	5	2
487	2	3	7	9	8	5	2
540	2	3	7	2	8	77	2

ST-8 Clonal Complex: cc8



Russell, J. E., Urwin, R., Gray, S. J., Fox, A. J., Feavers, I. M. & Maiden, M. C. (2008). Molecular epidemiology of meningococcal disease in England and Wales 1975-1995, before the introduction of serogroup C conjugate vaccines. *Microbiology* 154, 1170-1177.

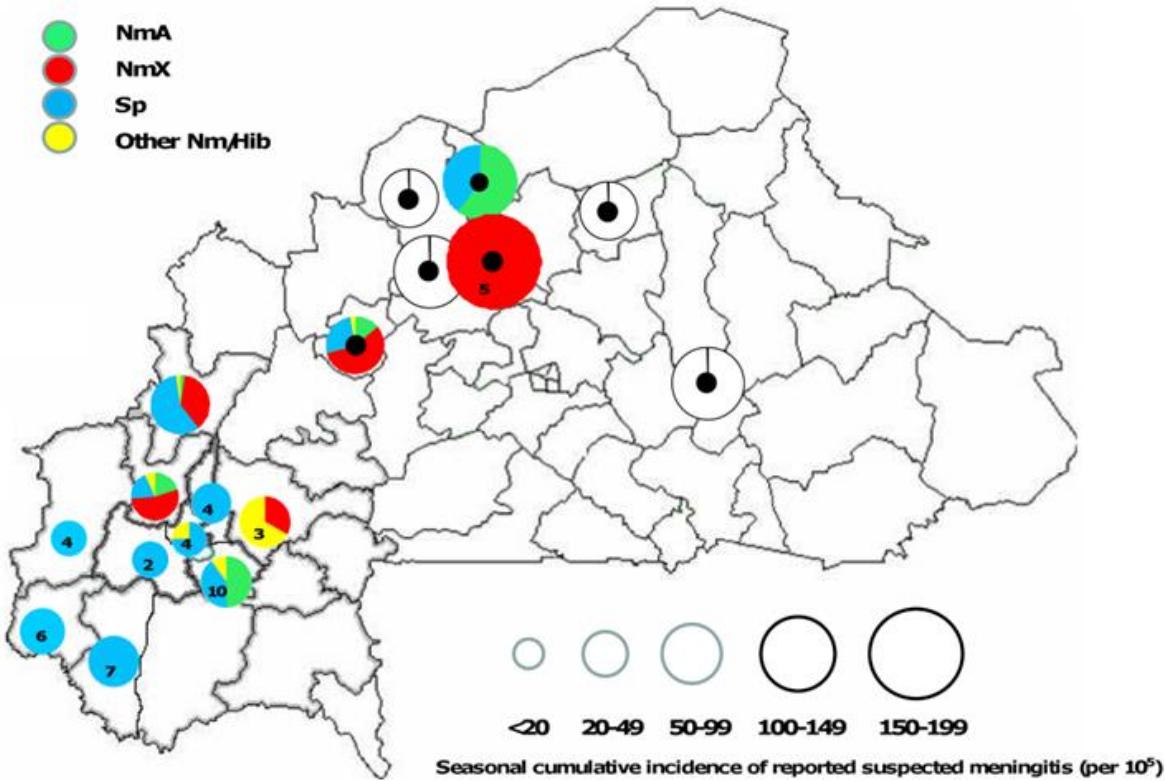
MenAfriCar: meningococcal type distribution in carriage



Ali, O., et al. and MenAfriCar Consortium. (2015) The Diversity of Meningococcal Carriage Across the African Meningitis Belt and the Impact of Vaccination With a Group A Meningococcal Conjugate Vaccine. *J Infect Dis* **212**, 1298-1307

Insert:
Keith: 3. Introduction to PubMLST typing and
serogroup X

Serogroup C, W, and X meningococcal disease occurs in Africa

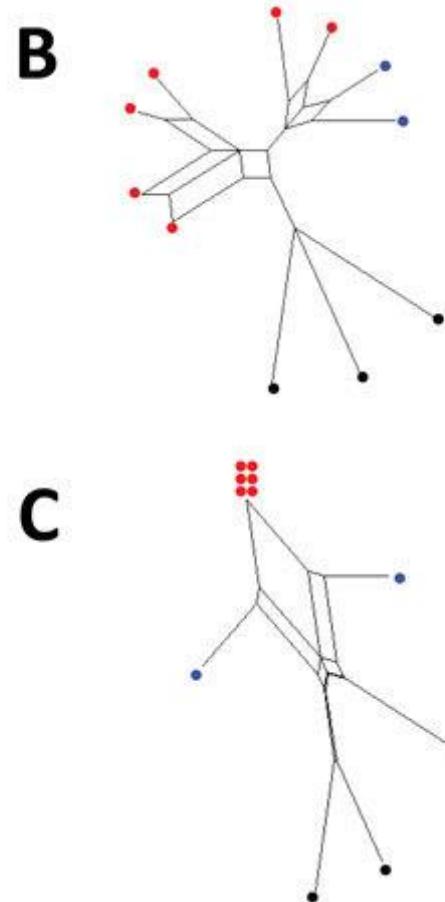
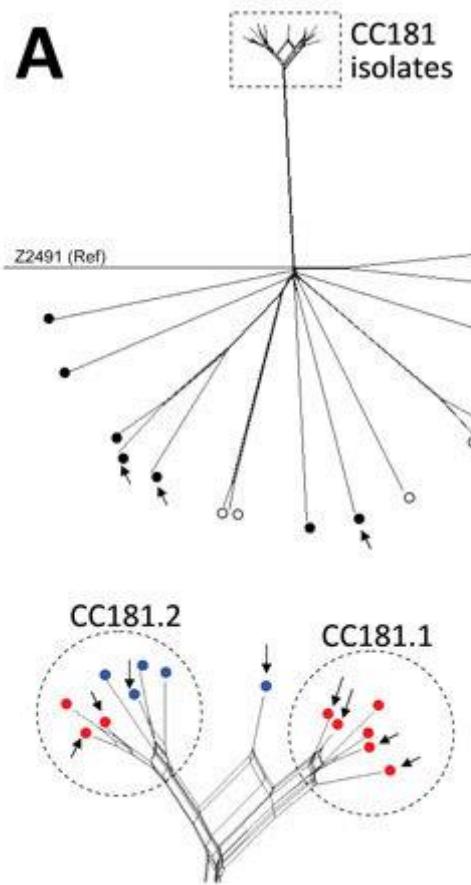


Wang, J. F., Caugant, D. A., Morelli, G., Koumaré, B. & Achtman, M. (1993). Antigenic and epidemiological properties of the ET-37 complex of *Neisseria meningitidis*. *Journal of Infectious Diseases* 167, 1320-1329.

Kwara, A., Adegbola, R. A., Corrah, P. T., Weber, M., Achtman, M., Morelli, G., Caugant, D. A. & Greenwood, B. M. (1998). Meningitis caused by a serogroup W135 clone of the ET-37 complex of *Neisseria meningitidis* in West Africa. *Trop Med Int Health* 3, 742-746.

Delrieu, I., Yaro, S., Tamekloe, T. A., Njanpop-Lafourcade, B. M., Tall, H., Jaillard, P., Ouedraogo, M. S., Badziklou, K., Sanou, O., Drabo, A., Gessner, B. D., Kambou, J. L. & Mueller, J. E. (2011). Emergence of epidemic *Neisseria meningitidis* serogroup X meningitis in Togo and Burkina Faso. *PLoS One* 6, e19513.

Meningococcal Serogroup X in sub-Saharan Africa



Key:

- White circles indicate carriage isolates;
- Black circles indicate invasive isolates obtained outside of Africa;
- Red circles indicate isolates obtained in sub-Saharan Africa since 2006;
- Blue circles indicate isolates obtained from sub-Saharan Africa during the 1990s.

Agnememel, A., Hong, E., Giorgini, D., Nunez-Samudio, V., Deghmane, A. E. & Taha, M. K. (2016). *Neisseria meningitidis* Serogroup X in Sub-Saharan Africa. *Emerg Infect Dis.* **22**, 698-702.

Section 2: From multi locus to whole genome

Molecular Approaches to Clinical Microbiology in Africa 2024

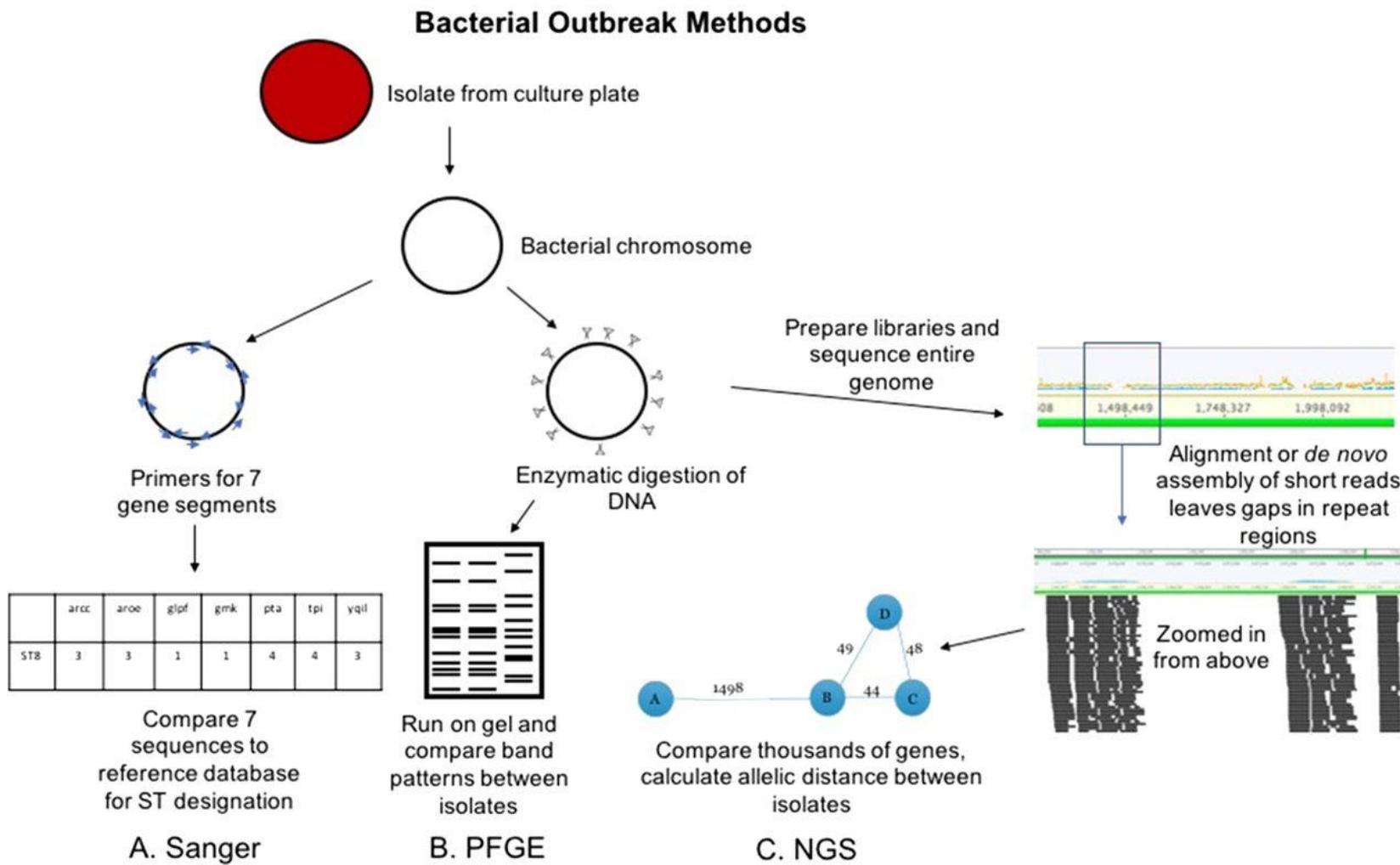
Martin Maiden

Department of Biology



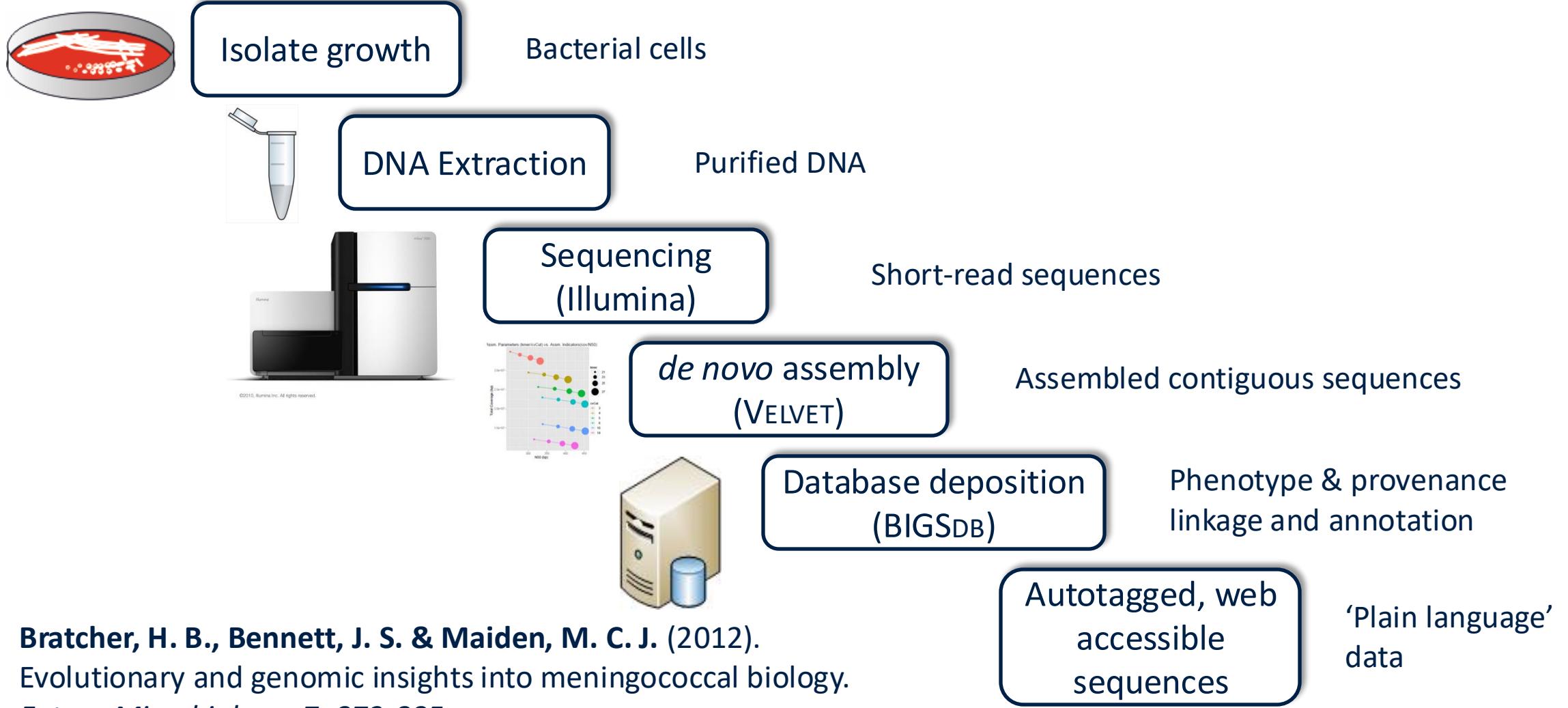
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OXFORD

Conventional and NGS methods for bacterial characterisation.

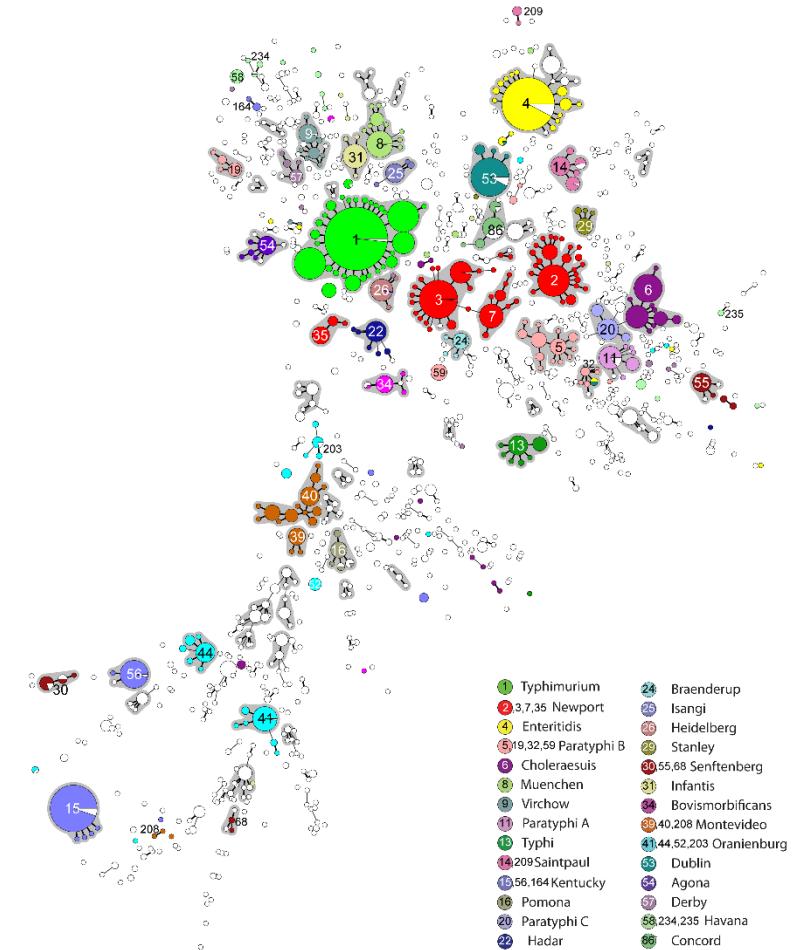
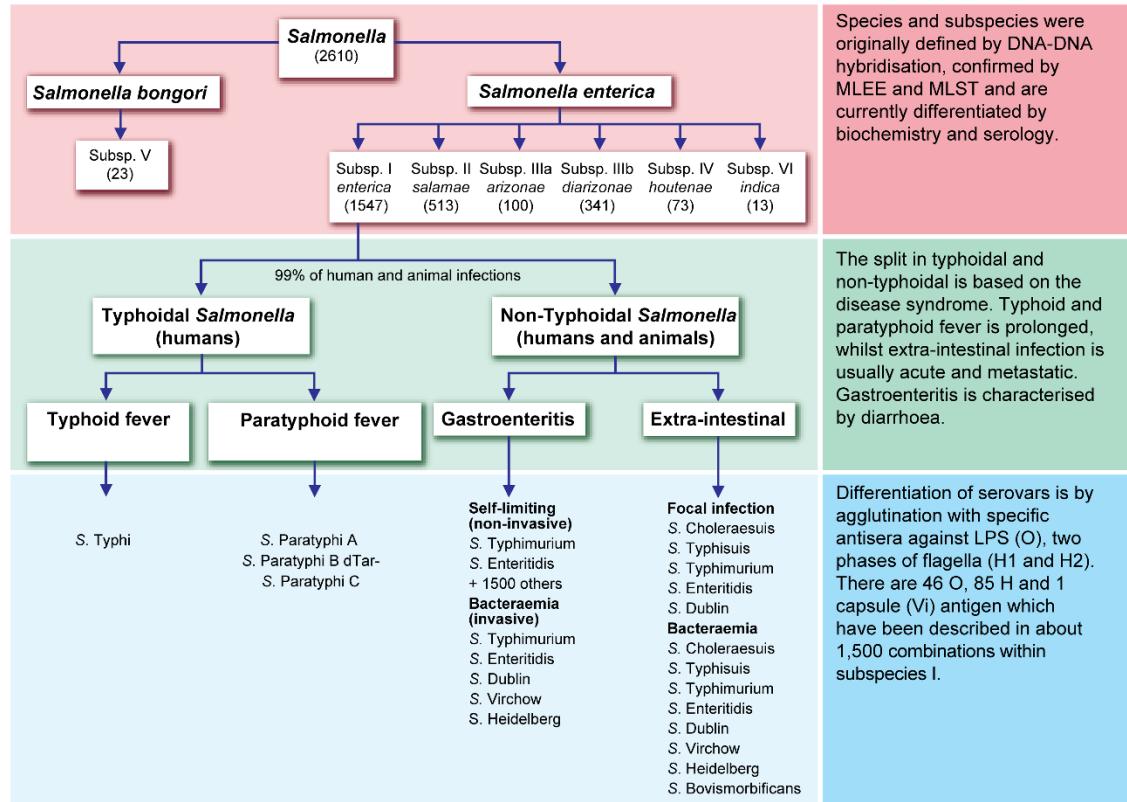


Dougherty, C.E. & Graf, E.
(2019). Conventional and NGS
methods for bacterial outbreak
investigation. *Clin. Lab. Sci.* **32**,
70-77.

Whole genome sequence pipeline



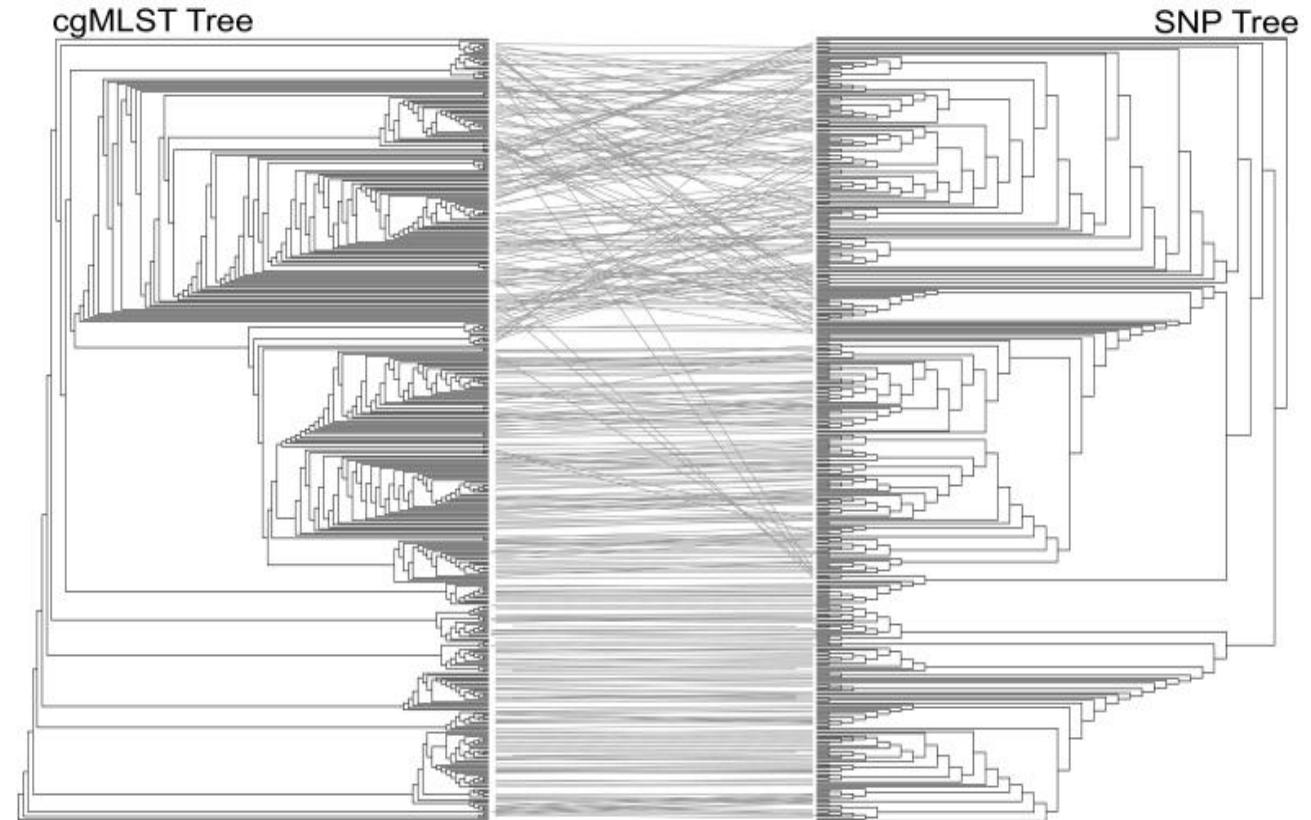
eBURST Groups: *Salmonella*



Achtman, M., Wain, J., Weill, F. X., Nair, S., Zhou, Z. M., Sangal, V., Krauland, M. G., Hale, J. L., Harbottle, H., Uesbeck, A., Dougan, G., Harrison, L. H., Brisse, S. & SEMS Group (2012). Multilocus Sequence Typing as a Replacement for Serotyping in *Salmonella enterica*. *Plos Pathogens*. 8, e1002776.

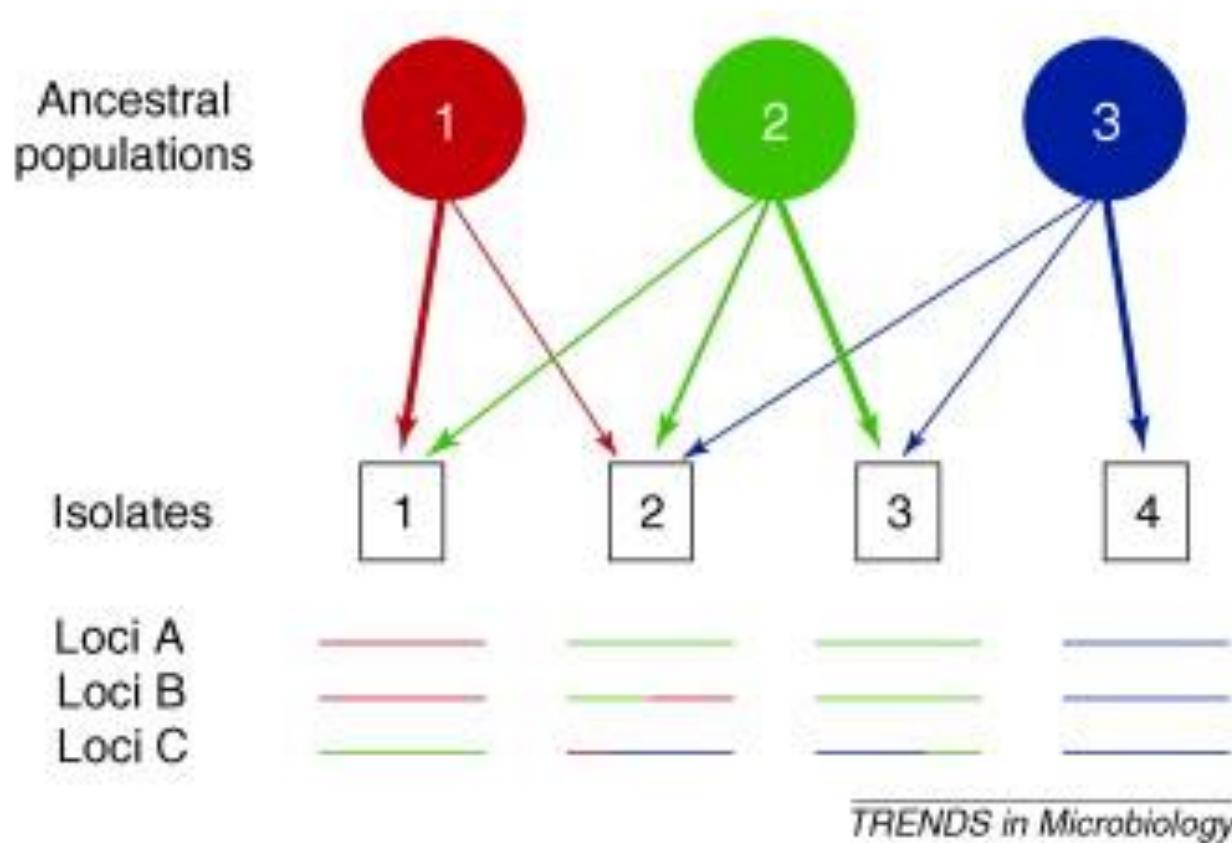
cgMLST vs 'core SNPs'

- Essentially based on the same data.
- cgMLST can be used to recover 'core SNPs'.
- cgMLST provides a stable nomenclature that is reference free.



Pearce, M. E., Alikhan, N. F., Dallman, T. J., Zhou, Z., Grant, K. & Maiden, M. C. J. (2018). Comparative analysis of core genome MLST and SNP typing within a European *Salmonella* serovar Enteritidis outbreak. *International Journal of Food Microbiology* 274, 1-11.

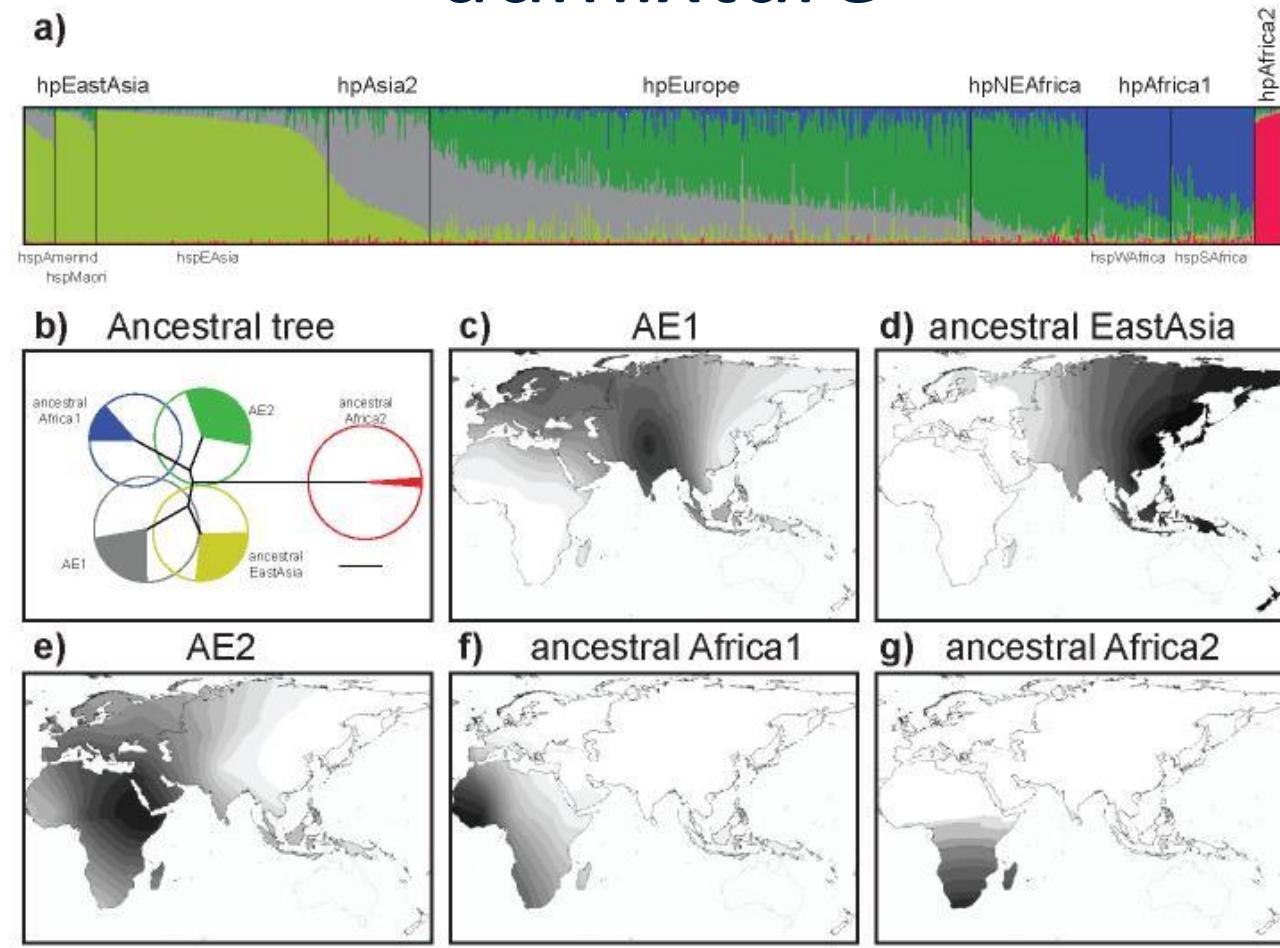
Population admixture: the STRUCTURE model



The top part shows the ancestral populations in distinct colors. The bottom part shows the genotypes of the isolates, with fragments colored according to their ancestral population of origin.

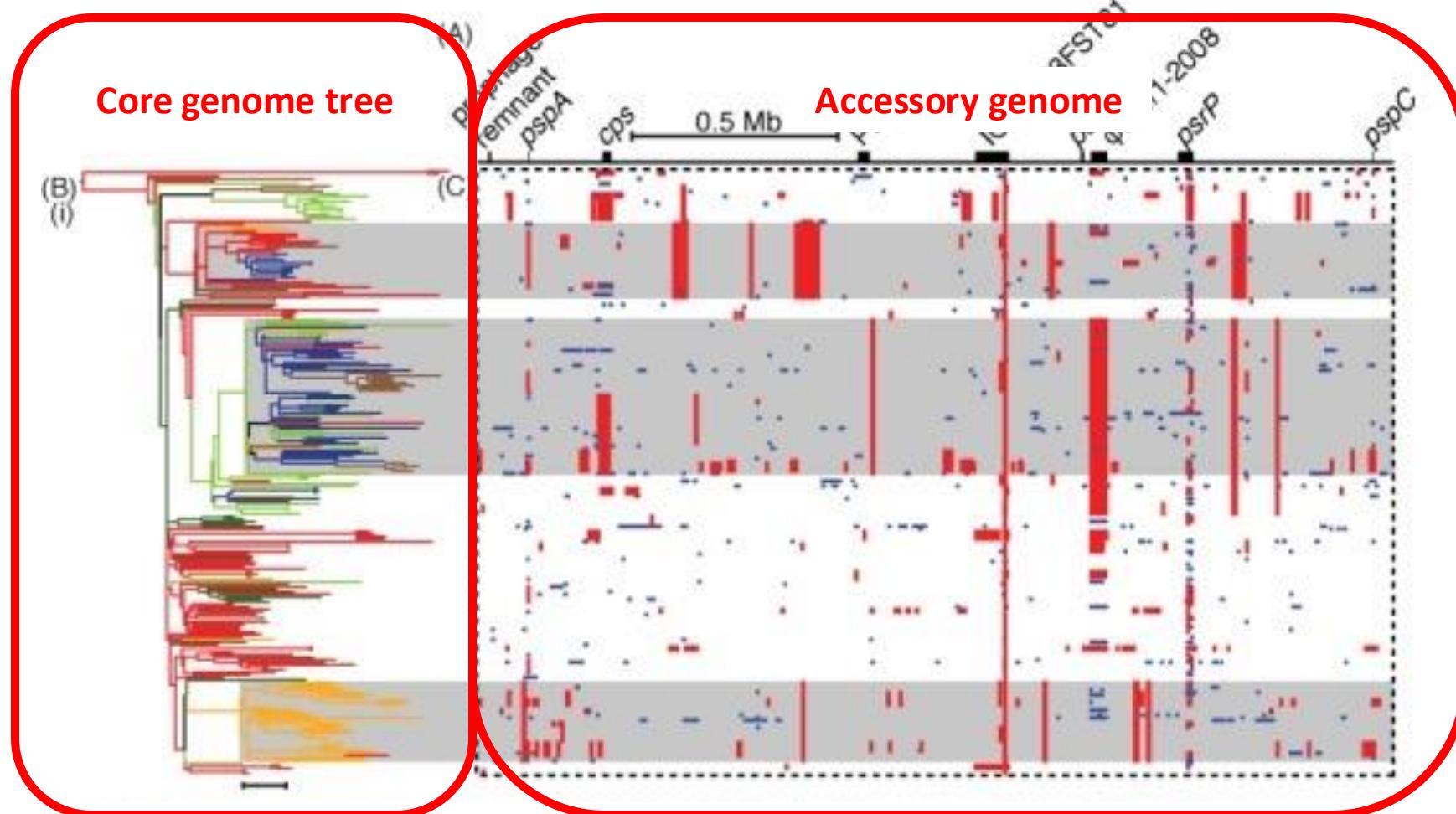
Didelot, X. & Maiden, M. C. (2010). Impact of recombination on bacterial evolution. *Trends in Microbiology* 18, 315-322.

Helicobacter pylori is non-clonal: phylogeography & admixture



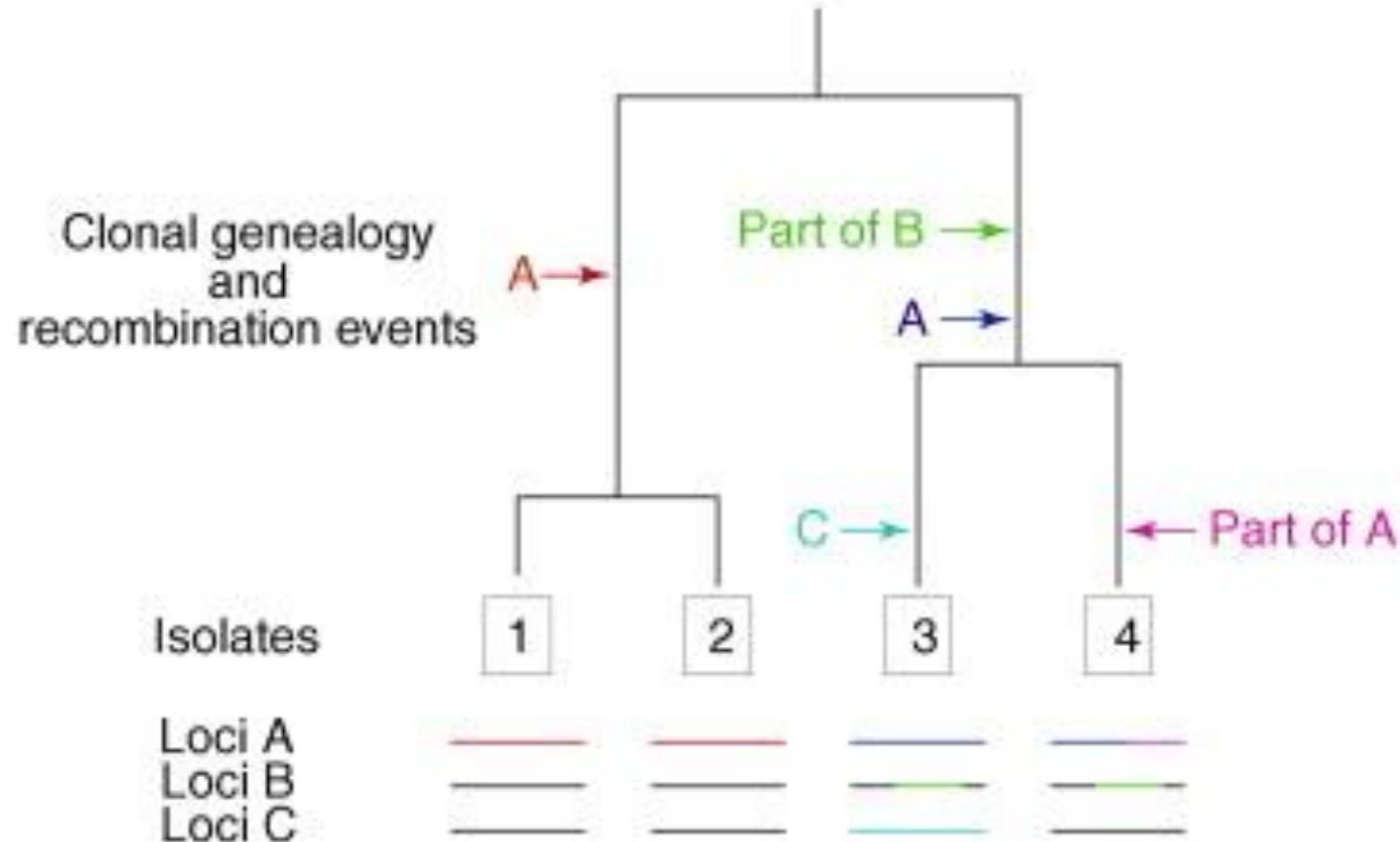
Linz, B., F. Balloux, Y. Moodley, A. Manica, H. Liu, P. Roumagnac, D. Falush, C. Stamer, F. Prugnolle, S. W. van der Merwe, Y. Yamaoka, D. Y. Graham, E. Perez-Trallero, T. Wadstrom, S. Suerbaum, and M. Achtman. (2007). An African origin for the intimate association between humans and *Helicobacter pylori*, *Nature*, 445: 915-8.

Gubbins: an analysis of PMEN1 clone



Croucher, N. J., Page, A. J., Connor, T. R., Delaney, A. J., Keane, J. A., Bentley, S. D., Parkhill, J. & Harris, S. R. (2015). Rapid phylogenetic analysis of large samples of recombinant bacterial whole genome sequences using Gubbins. *Nucleic acids research* 43, e15.

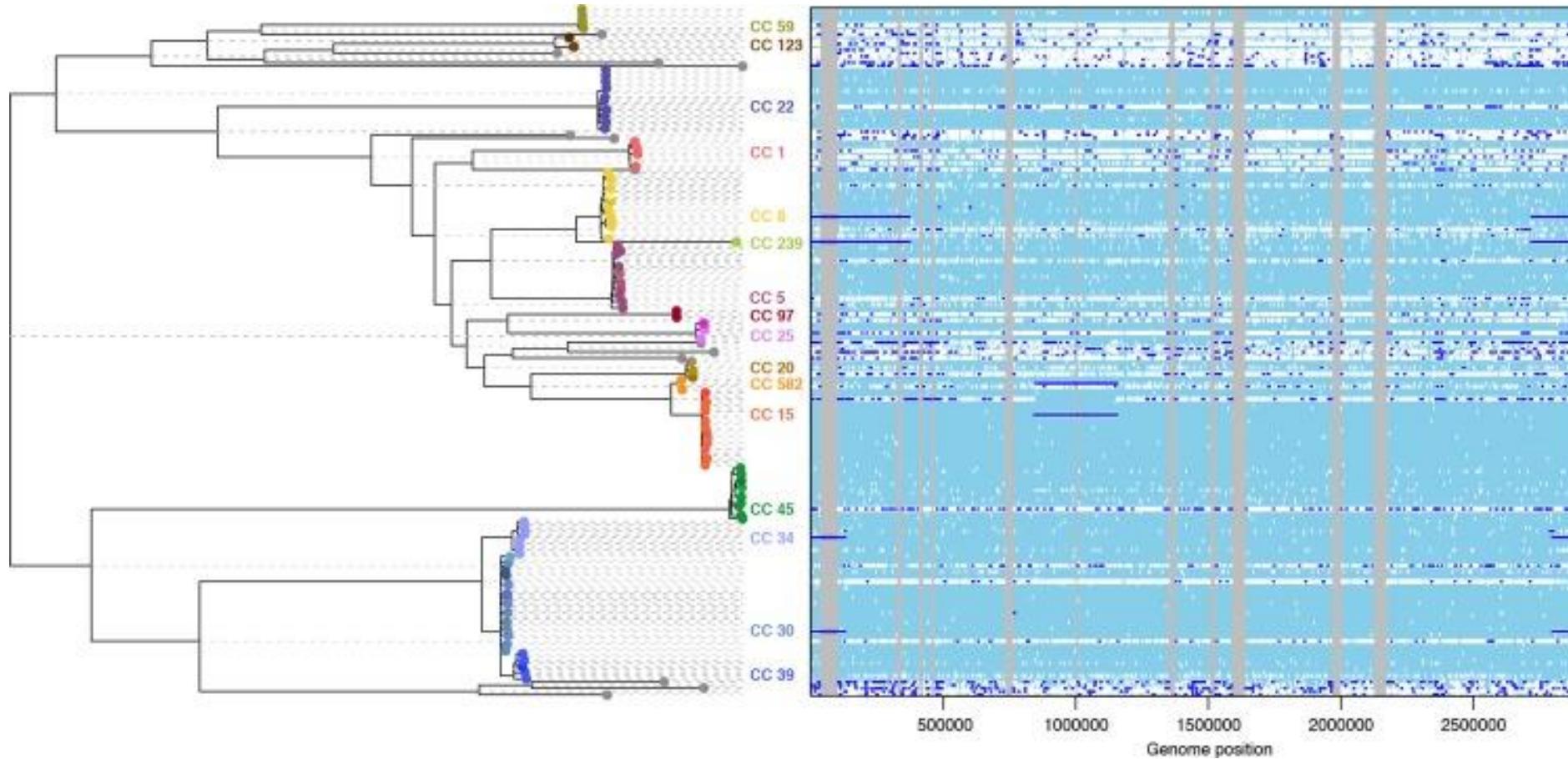
The ClonalFrame Model



TRENDS in Microbiology

Didelot, X. & Maiden, M. C. (2010). Impact of recombination on bacterial evolution. *Trends in Microbiology* 18, 315-322.

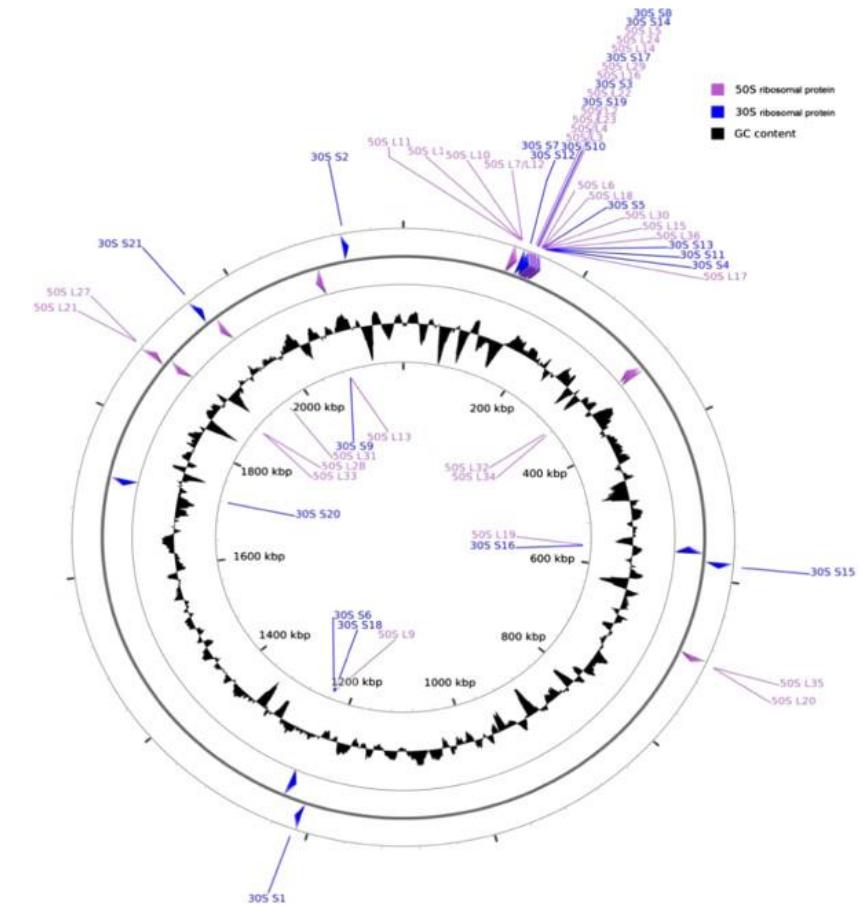
ClonalFrameML: recombination in *S. aureus*



Didelot, X. & Wilson, D. J. (2015). ClonalFrameML: Efficient Inference of Recombination in Whole Bacterial Genomes. *PLoS Computational Biology* 11, e1004041.

Ribosomal MLST (rMLST)

- Ribosomal MLST provides a universal characterisation scheme
 - ‘from domain to strain’.
- Most bacteria have 53 protein subunits,
 - variation of the *rps* genes are used just as for conventional MLST loci.
 - These loci are least affected by HGT.
- This provides highly accurate species identification,
 - but does rely on WGS data.



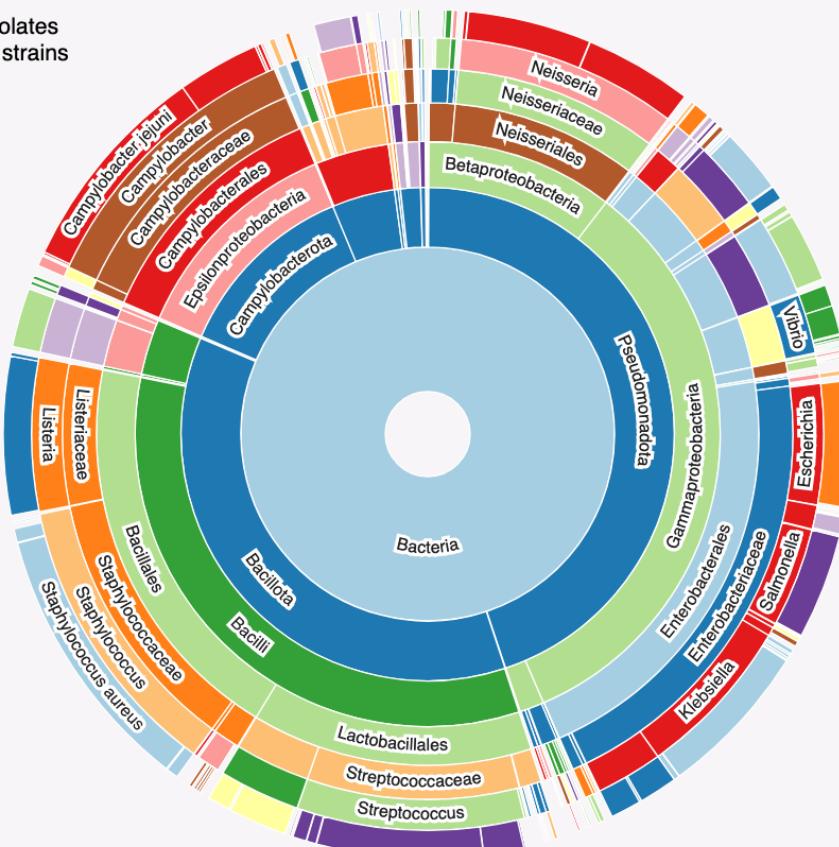
Jolley, K. A., Bliss, C. M., Bennett, J. S., Bratcher, H. B., Brehony, C. M., Colles, F. M., Wimalaratna, H. M., Harrison, O. B., Sheppard, S. K., Cody, A. J. & Maiden, M. C. (2012). Ribosomal Multi-Locus Sequence Typing: universal characterization of bacteria from domain to strain. *Microbiology*. **158**, 1005-1015.

Ribosomal MLST

IDENTIFY SPECIES

Genome taxonomic coverage

- all isolates
- type strains



Click on any arc to zoom in. Click on centre circle to zoom out. Click on background to reset zoom.

'Type strains' include exemplar records where no formal type strain has been defined.

Ribosomal Multilocus Sequence Typing (rMLST) is an approach that indexes variation of the 53 genes encoding the bacterial ribosome protein subunits (*rps* genes) as a means of integrating microbial taxonomy and typing.

The *rps* gene variation catalogued in this database permits rapid identification of the phylogenetic position of any bacterial sequence at the domain, phylum, class, order, family, genus, species and strain levels.

rMLST is described in Jolley et al. 2012 *Microbiology* 158:1005-15.

Databases curated by James Bray.

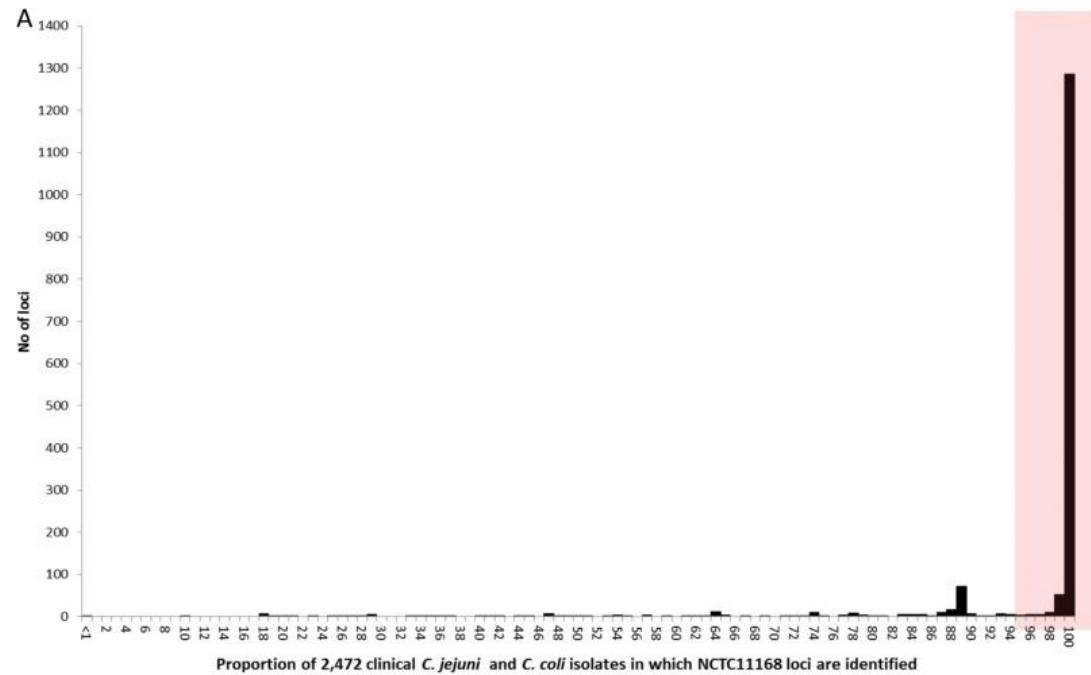
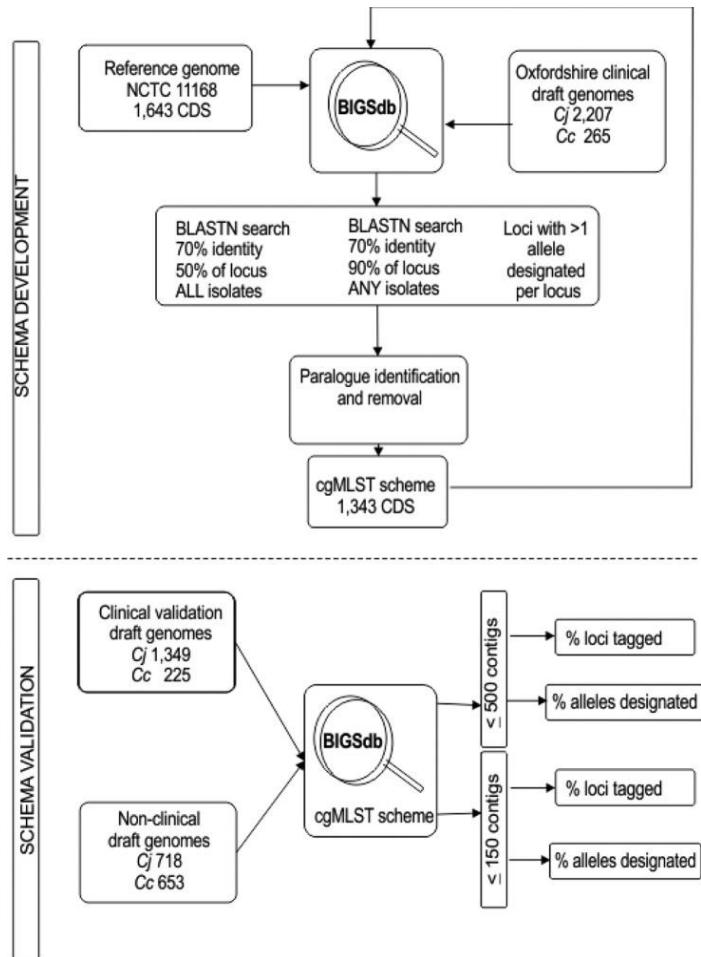
For academic non commercial use only. For full terms and conditions please see [rMLST_licence.pdf](#). To discuss any other sort of use, including a commercial use licence, please contact innovation@innovation.ox.ac.uk quoting reference 7895/MC.

Access to the databases can be obtained by [registering for a PubMLST account](#) and making the request via the registration system.

- Taxonomic coverage of the databases
- Programmatic access to the species identification tool
- Upload your own genome data privately to a scratch database for analysis
- Description of species identification method



Defining a core genome



Cody, A. J., Bray, J. E., Jolley, K. A., McCarthy, N. D. & Maiden, M. C. J. (2017). Core Genome Multilocus Sequence Typing Scheme for Stable, Comparative Analyses of *Campylobacter jejuni* and *C. coli* Human Disease Isolates. *J Clin Microbiol* 55, 2086-2097.

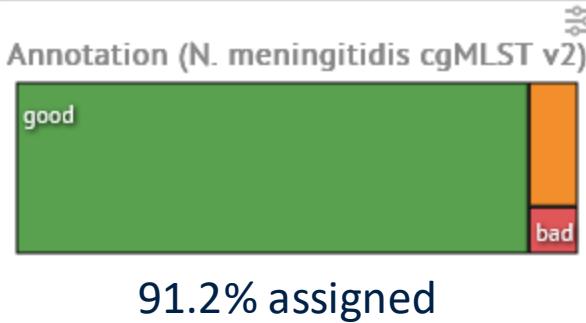
Meningococcal cgMLST schemes

- v1 developed in 2014, 1605 loci,
 - up to 50 missing loci allowed for a cgMLST.
- v2 finalized in 2022 (implemented on PubMLST): 1422 loci,
 - up to 25 missing loci allowed for a cgMLST.
- Problems with v2:
 - inconsistent start sites (especially among different species);
 - multiple consecutive start sites, e.g. ATGATGATG that are not completely conserved;
 - inconsistent end sites where a stop codon is present near the end of a sequence.
- v3 developed by:
 - curating loci to ensure consistent start sites;
 - removing loci that resulted in ‘double hits’;
 - removing loci that were missing in more than 2% of genomes.
- V3 comprised 1329 loci,
 - up to 25 missing loci allowed for a cgMLST.
- For the purposes of stable typing, the number of loci is less important than their reliability.
- In practise, the differences in the schemes is marginal in terms of resolution.

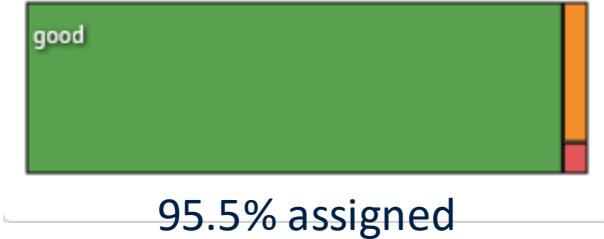
Bratcher, H. B., Corton, C., Jolley, K. A., Parkhill, J. & Maiden, M. C. (2014). A gene-by-gene population genomics platform: *de novo* assembly, annotation and genealogical analysis of 108 representative *Neisseria meningitidis* genomes. BMC Genomics 15, 1138.

Relative performance of cgMLST schemes v2 and v3

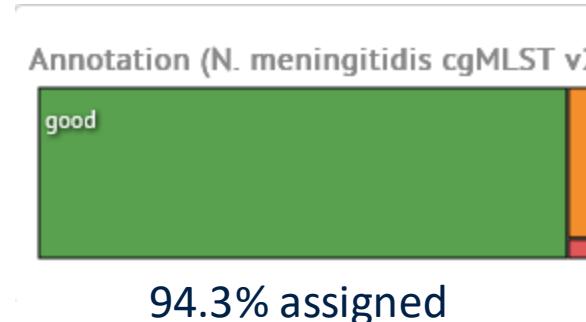
All Nm genomes >2Mbp, 0 Ns (n=41,467)



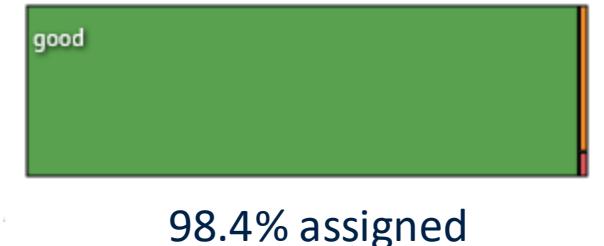
Annotation (N. meningitidis cgMLST v3)



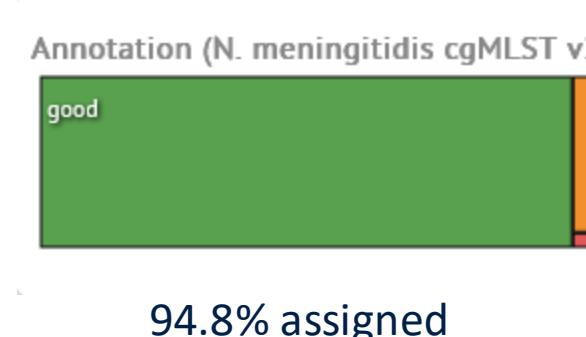
Nm genomes with >2 Mbp, <= 300 contigs, 0 Ns (n=36,409)



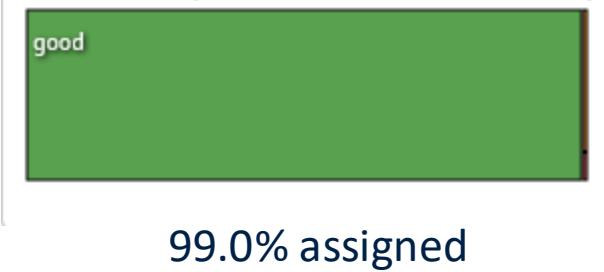
Annotation (N. meningitidis cgMLST v3)



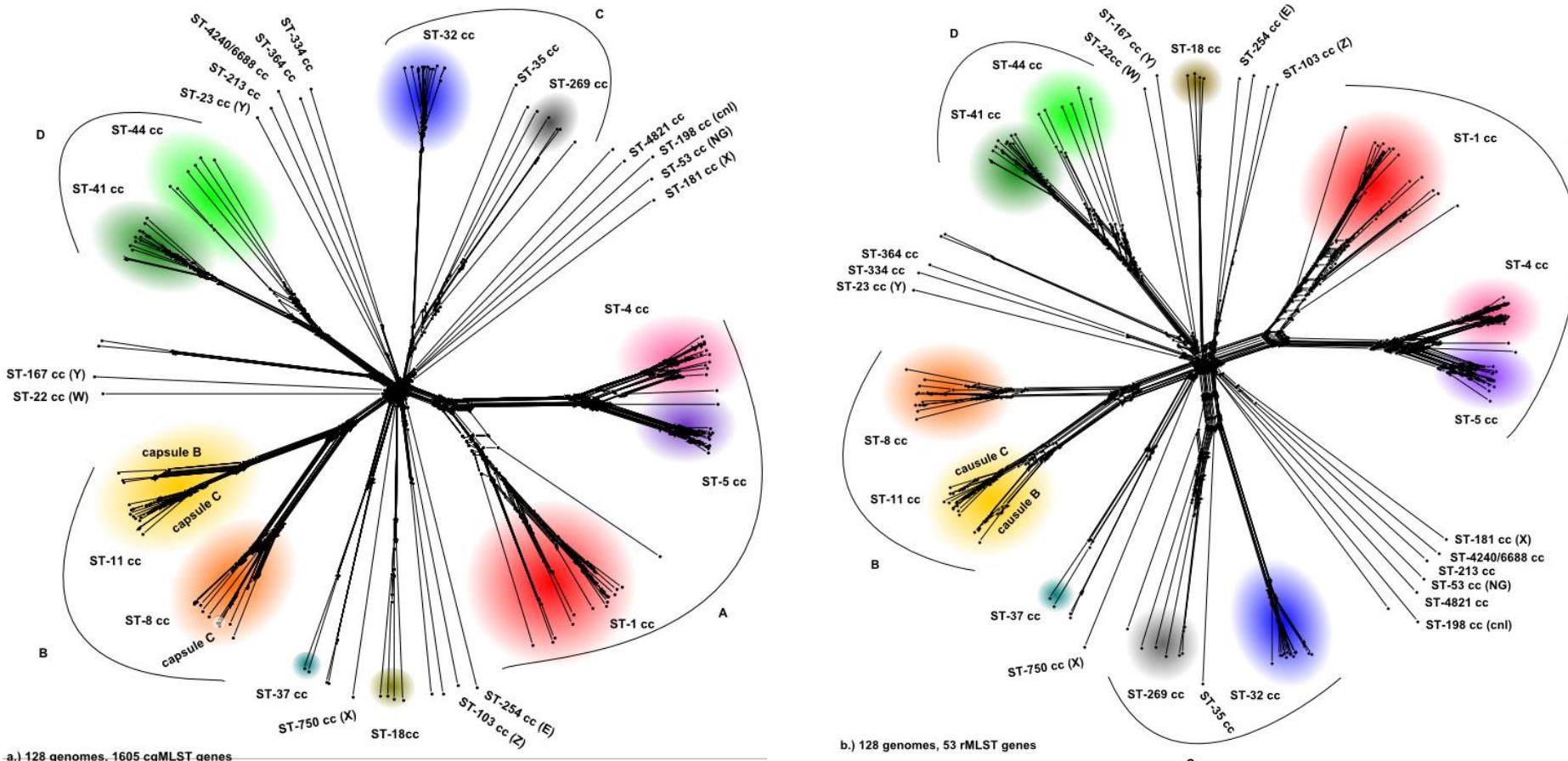
Nm genomes with >2 Mbp, <= 200 contigs, 0 Ns (n=29,078)



Annotation (N. meningitidis cgMLST v3)



Increasing data increases resolution

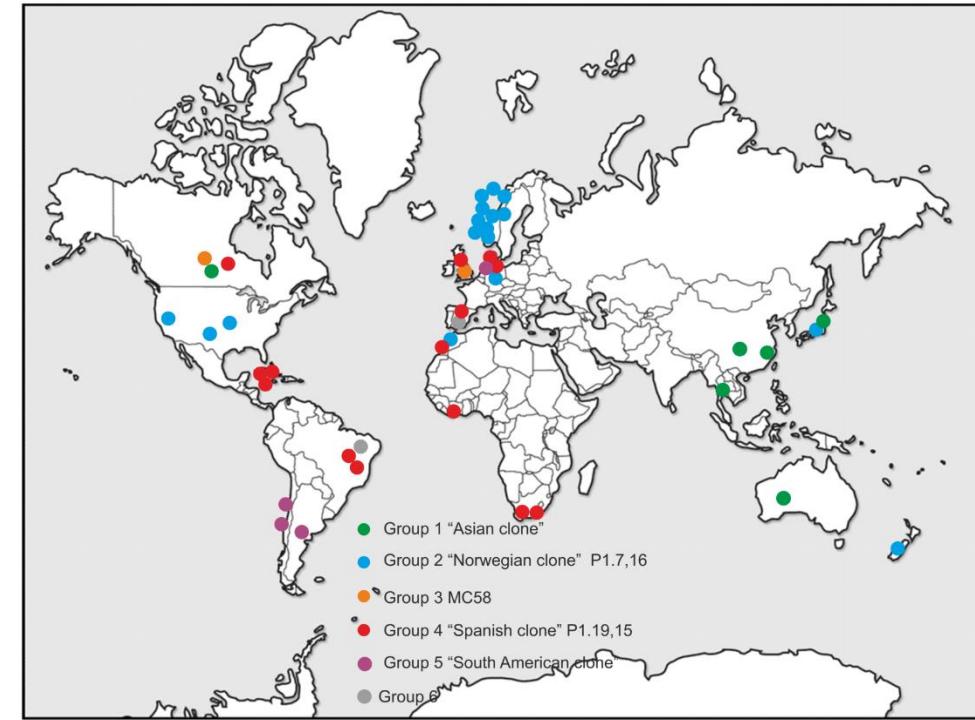


Bratcher, H. B., Corton, C., Jolley, K. A., Parkhill, J. & Maiden, M. C. (2014). A gene-by-gene population genomics platform: *de novo* assembly, annotation and genealogical analysis of 108 representative *Neisseria meningitidis* genomes. *BMC Genomics* **15, 1138.**

Global epidemiology of meningococcal disease

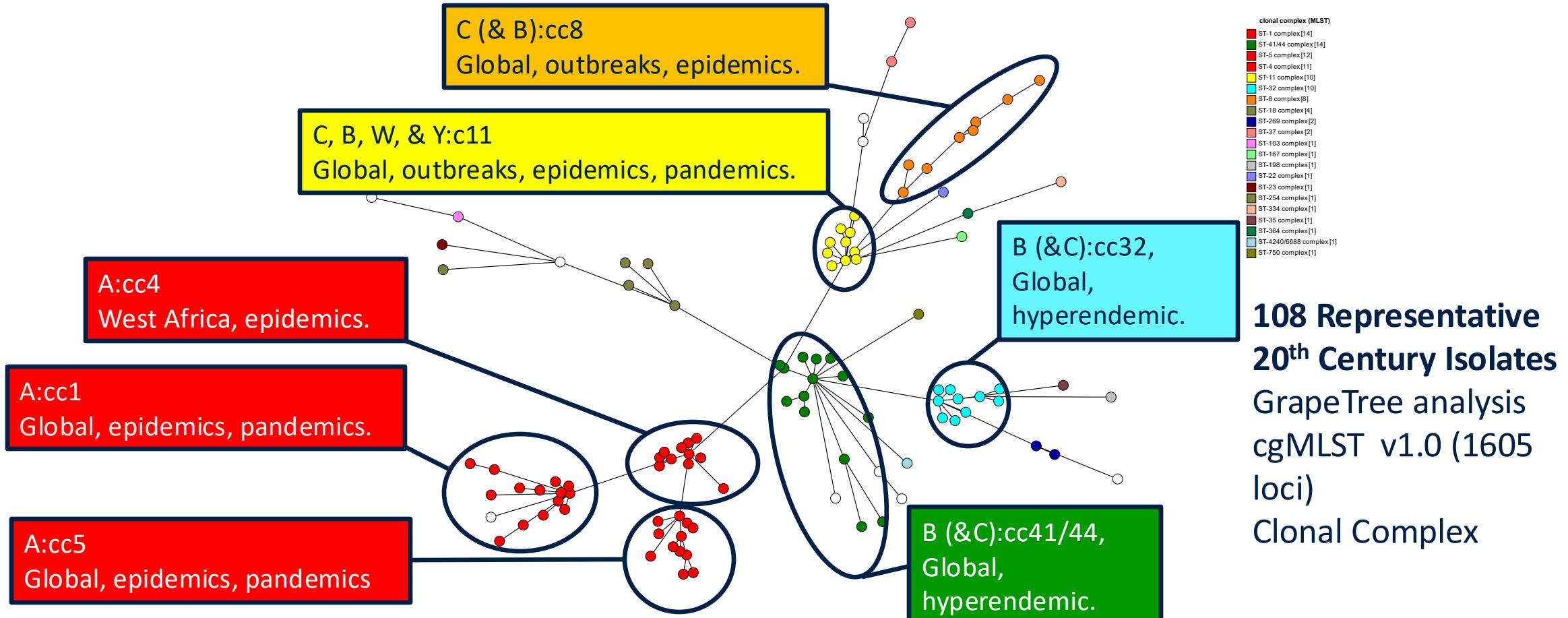
- **Endemic disease (multiple types):**
 - globally distributed;
 - 0.1 - 5 cases per 100,000.
- **Hyperendemic disease (e.g B:cc32; B:cc41/44):**
 - Local (community), national, global;
 - ~10 cases per 100,000.
- **Disease outbreaks (e.g. C:cc11; W:cc11):**
 - local & institutional (army camp, university).
- **Epidemic/pandemic disease (e.g. A:cc5):**
 - Regional, national, & global;
 - 500 cases per 100,000, or more.

Harrison, L. H., Trotter, C. L. & Ramsay, M. E. (2009).
Global epidemiology of meningococcal disease. *Vaccine* 27, B51-B63.



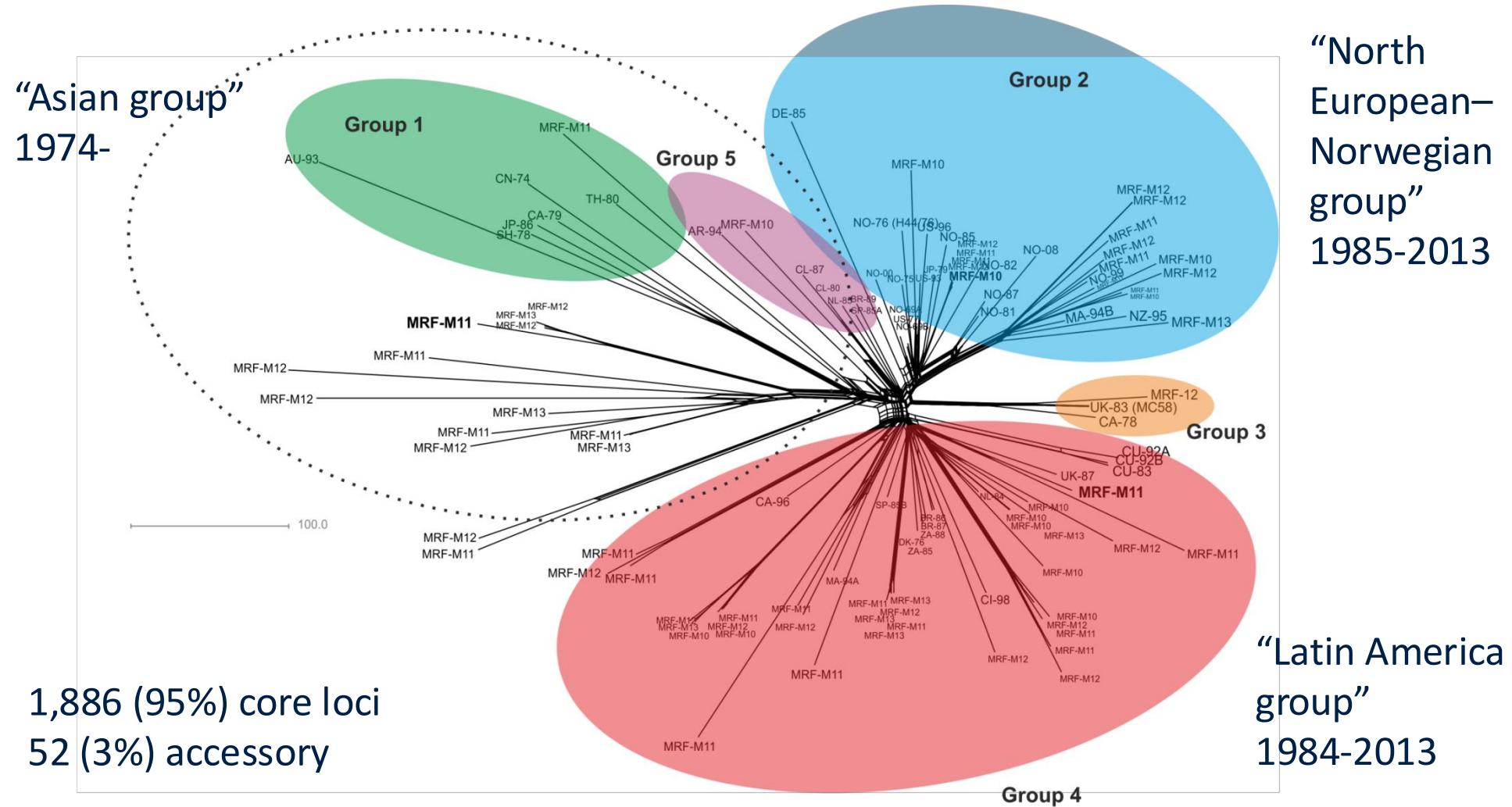
Harrison, O. B., Bray, J. E., Maiden, M. C. & Caugant, D. A. (2015). Genomic Analysis of the Evolution and Global Spread of Hyper-invasive Meningococcal Lineage 5. *EBioMedicine* 2, 234-243.

Age of Molecular Epidemiology: meningococcal disease in the 20th Century



Bratcher, H. B., Corton, C., Jolley, K. A., Parkhill, J. & Maiden, M. C. (2014). A gene-by-gene population genomics platform: *de novo* assembly, annotation and genealogical analysis of 108 representative *Neisseria meningitidis* genomes. *BMC Genomics*. **15**, 1138.

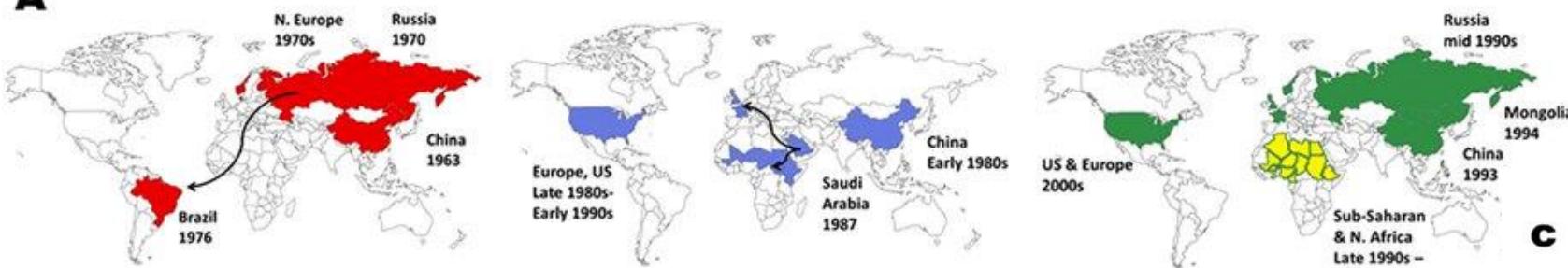
Global Lineage 5 (ET-5, cc32) hyperendemic



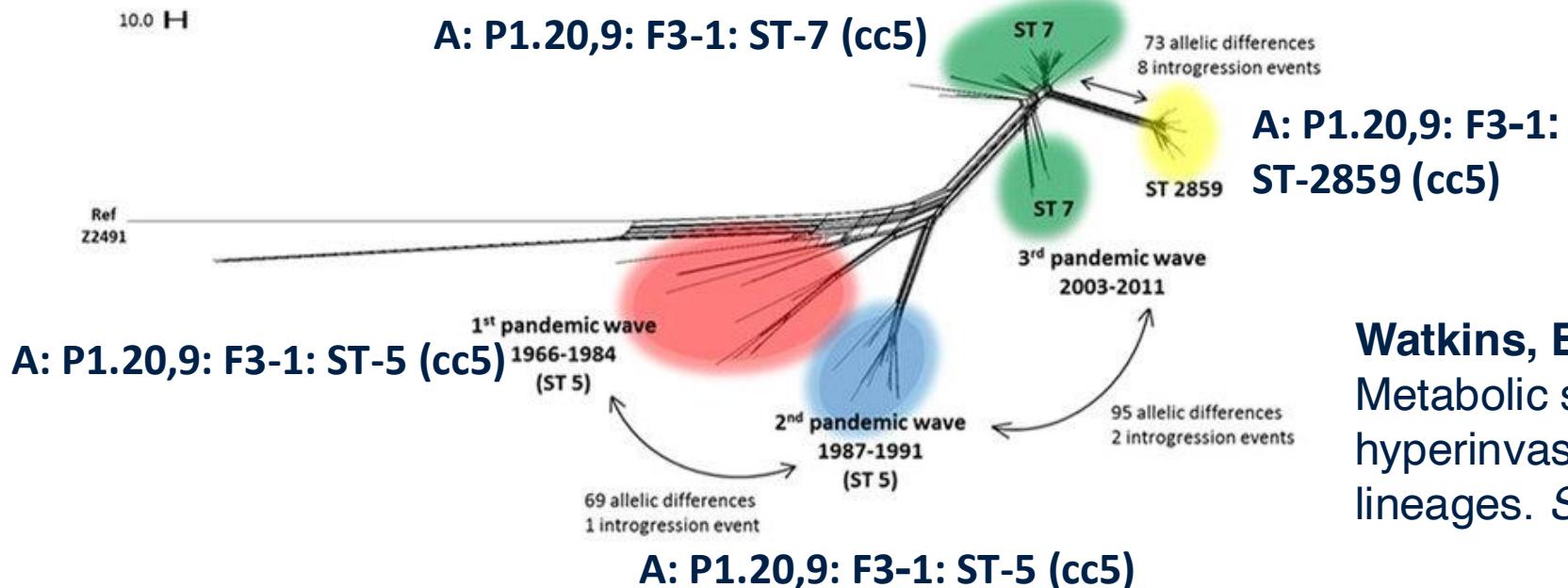
Harrison, O. B., Bray, J. E., Maiden, M. C. & Caugant, D. A. (2015). Genomic Analysis of the Evolution and Global Spread of Hyper-invasive Meningococcal Lineage 5. *EBioMedicine* 2, 234-243.

A:cc5 Pandemics: stable variants

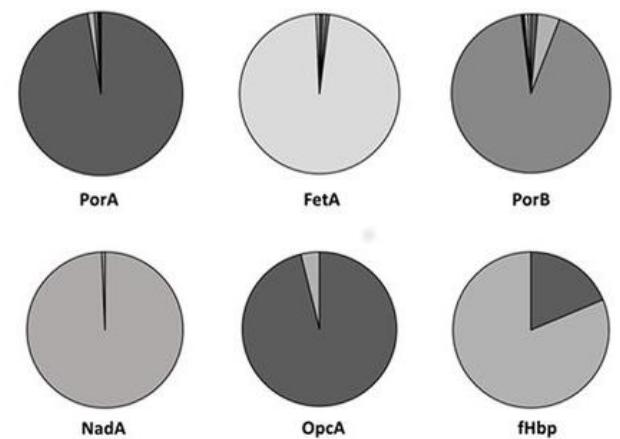
A



B



C



Watkins, E. R. & Maiden, M. C. (2017).
Metabolic shift in the emergence of
hyperinvasive pandemic meningococcal
lineages. *Scientific reports* 7, 41126.

Search or browse database

Enter search criteria or leave blank to browse all records. Modify form parameters to filter or enter a list of values.

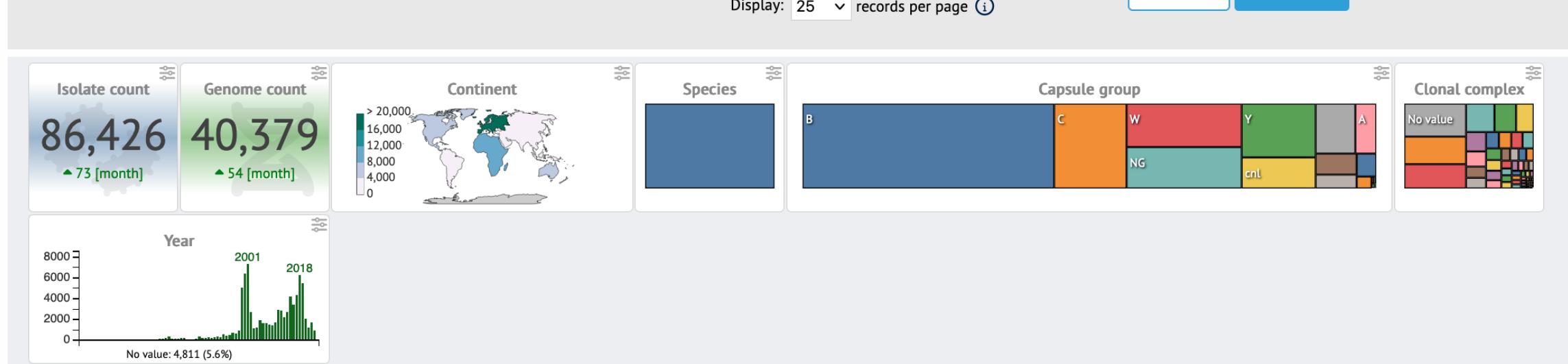
Isolate provenance/primary metadata fields

species = Neisseria meningitidis

Display/sort options

Order by: id ascending

Display: 25 records per page

[RESET](#)[SEARCH](#)

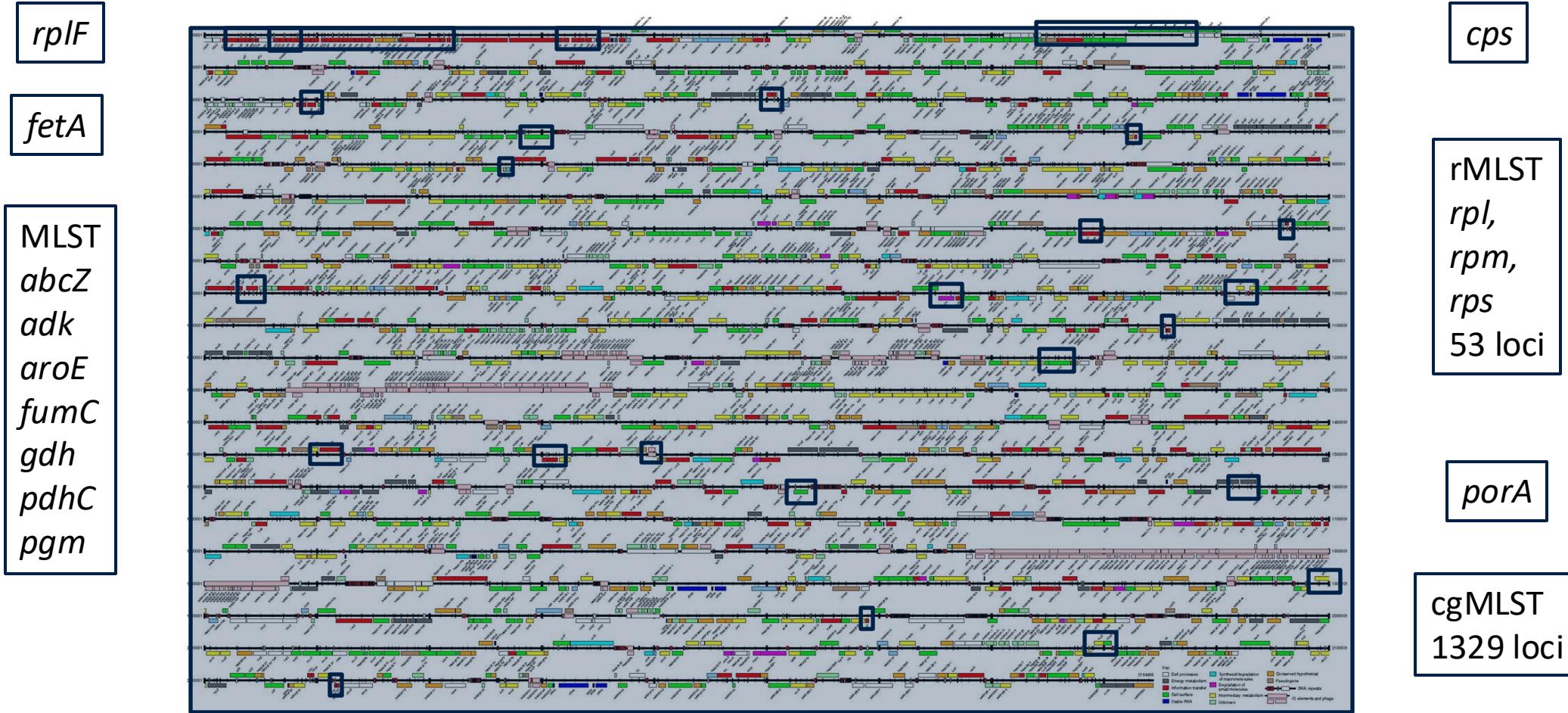
86,426 records returned (1 - 25 displayed). Click the hyperlinks for detailed information.

Your projects [Bookmark query](#)

[Add to project](#)[Bookmark](#)[«](#)[1 2 3 4 5 6](#)[»](#)

Source: <https://PubMLST.org/neisseria> 4th September 2023

Summary: typing targets in the meningococcal genome



Parkhill, J., Achtman, M., et al. Spratt, B. G. & Barrell, B. G. (2000). Complete DNA sequence of a serogroup A strain of *Neisseria meningitidis* Z2491. *Nature* **404**, 502-506.
Bratcher, H. B., Corton, C., Jolley, K. A., Parkhill, J. & Maiden, M. C. (2014). A gene-by-gene population genomics platform: *de novo* assembly, annotation and genealogical analysis of 108 representative *Neisseria meningitidis* genomes. *BMC Genomics* **15**, 1138.