

The background of the slide is a photograph showing the silhouettes of several large, historic buildings in Oxford, England, against a bright, golden-yellow sky. The most prominent features are a large dome on the left and a tall, pointed spire in the center. Other smaller spires and architectural details are visible in the distance.

**The population biology of bacterial pathogens  
and its importance for vaccination strategies**

**ADVAC 2014**

**Richard Moxon: University of Oxford**

# Rationale

- Vaccine strategies are primarily based on epidemiology: **burden of disease on hosts**
- Bacterial infections are often attributable to a particular microbe (e.g. pneumococcus, TB, anthrax etc.) often considered a **“species”**
- The **“species”** concept is useful, but complex; how to classify natural populations of bacteria and their **variations** (genotype and phenotype)

# **Why is the evolution of microbial variation important in vaccinology?**

**Selection of vaccine candidates and the immune responses to these antigens must take into account variations in the natural population over time and in differing geographical locations.**

# Outline of talk

## Part 1

- population and evolutionary biology of bacteria – some general considerations
- some exemplar diseases to illustrate complexities of population biology of selected bacterial pathogens
- challenge of vaccines against Serogroup B *Neisseria meningitidis* (meningococcus) and how knowledge of population biology might be applied

# Outline of talk

## Part 1

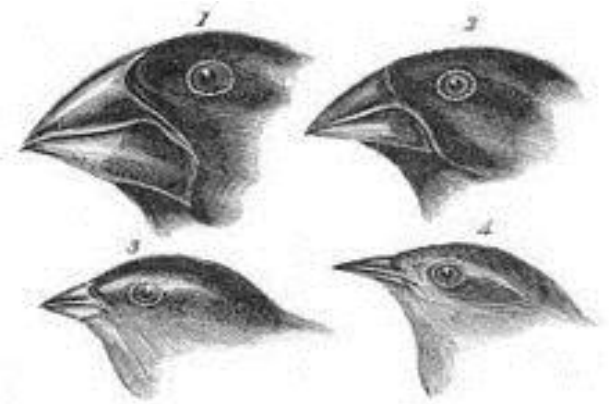
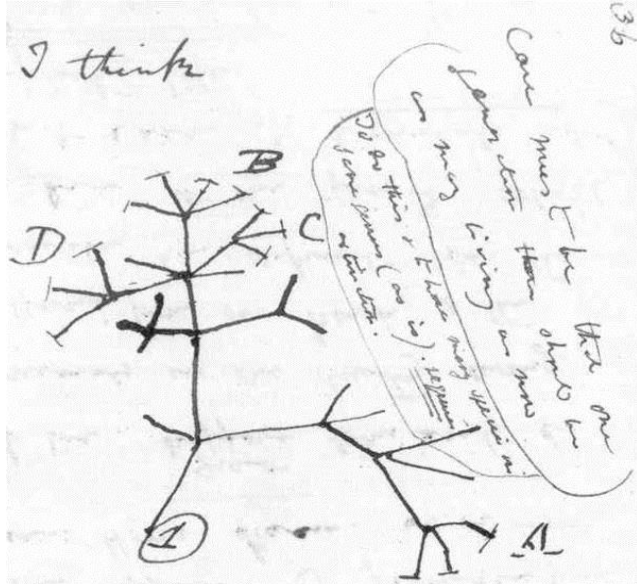
- population and evolutionary biology of bacteria – some general considerations
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# Theodosius Dobzhansky

**“Nothing in biology makes sense, except  
in the light of evolution”**

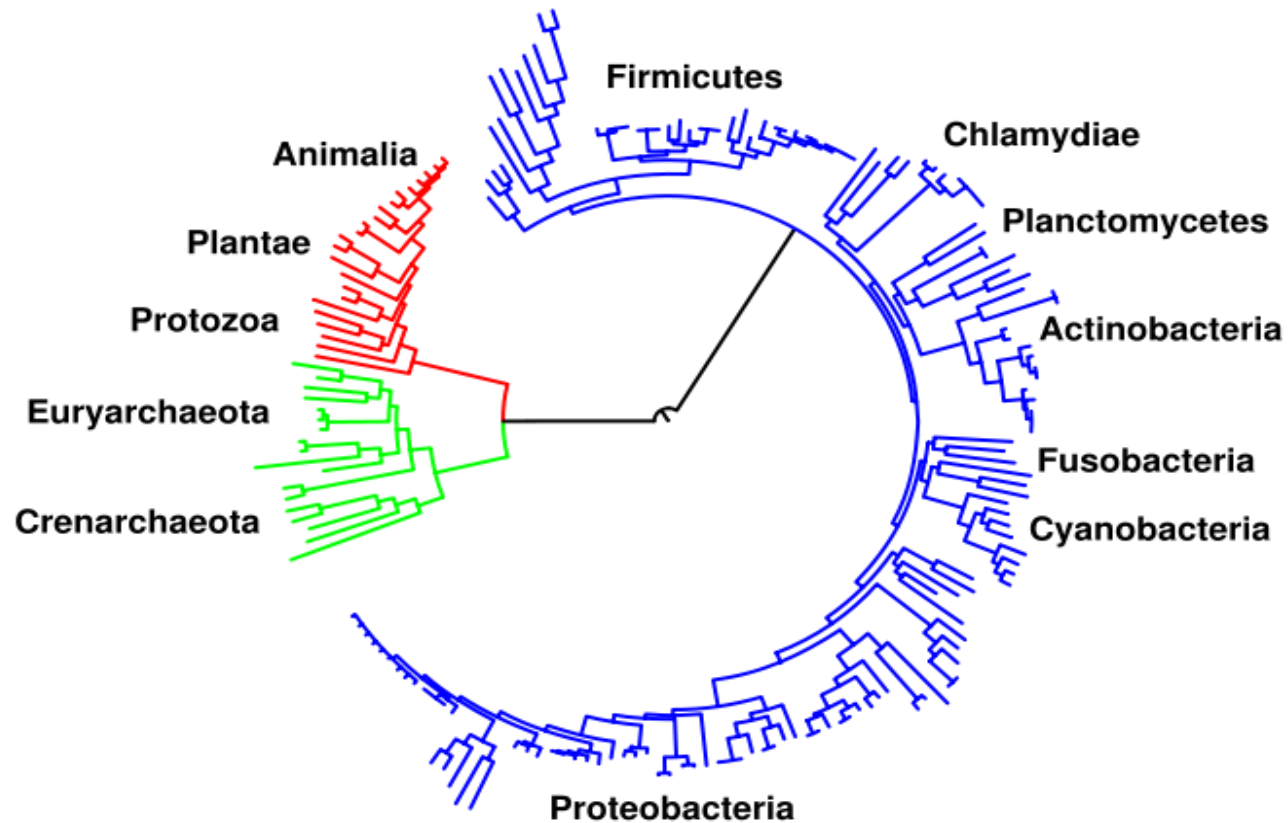
# Key concepts

- **Three domains of life: bacteria pre-date and outnumber their hosts**
- **Complexity of species concept and its implications for natural variation. Sex!**



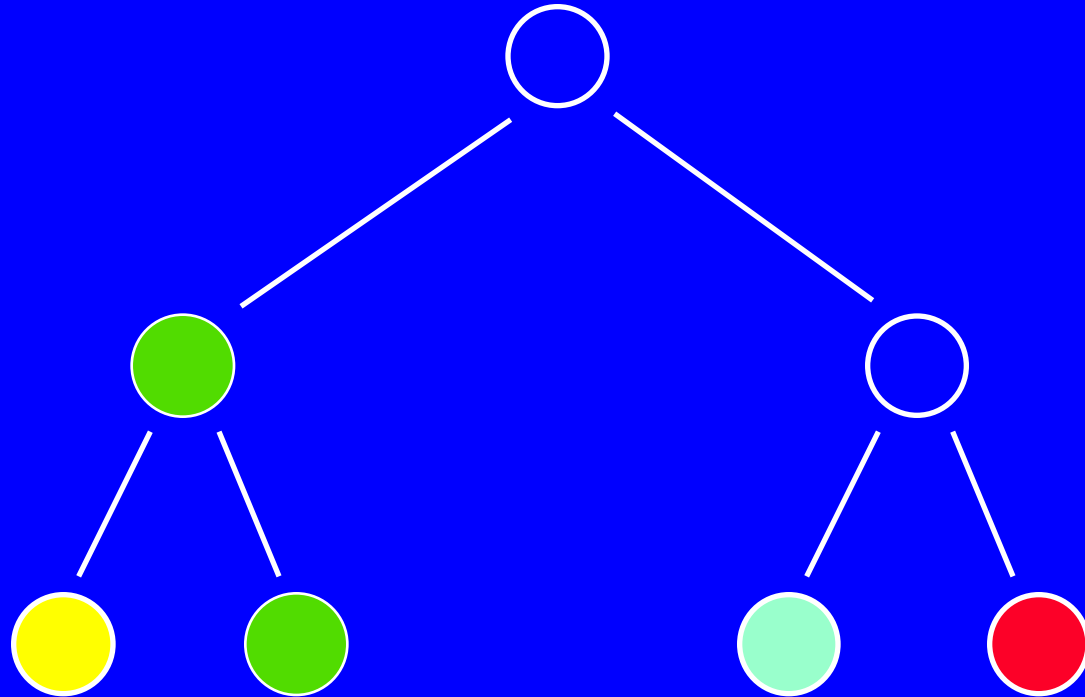
1. Geospiza magnirostris
2. Geospiza fortis
3. Geospiza parvula
4. Certhidea olivacea

Finches from Galapagos Archipelago

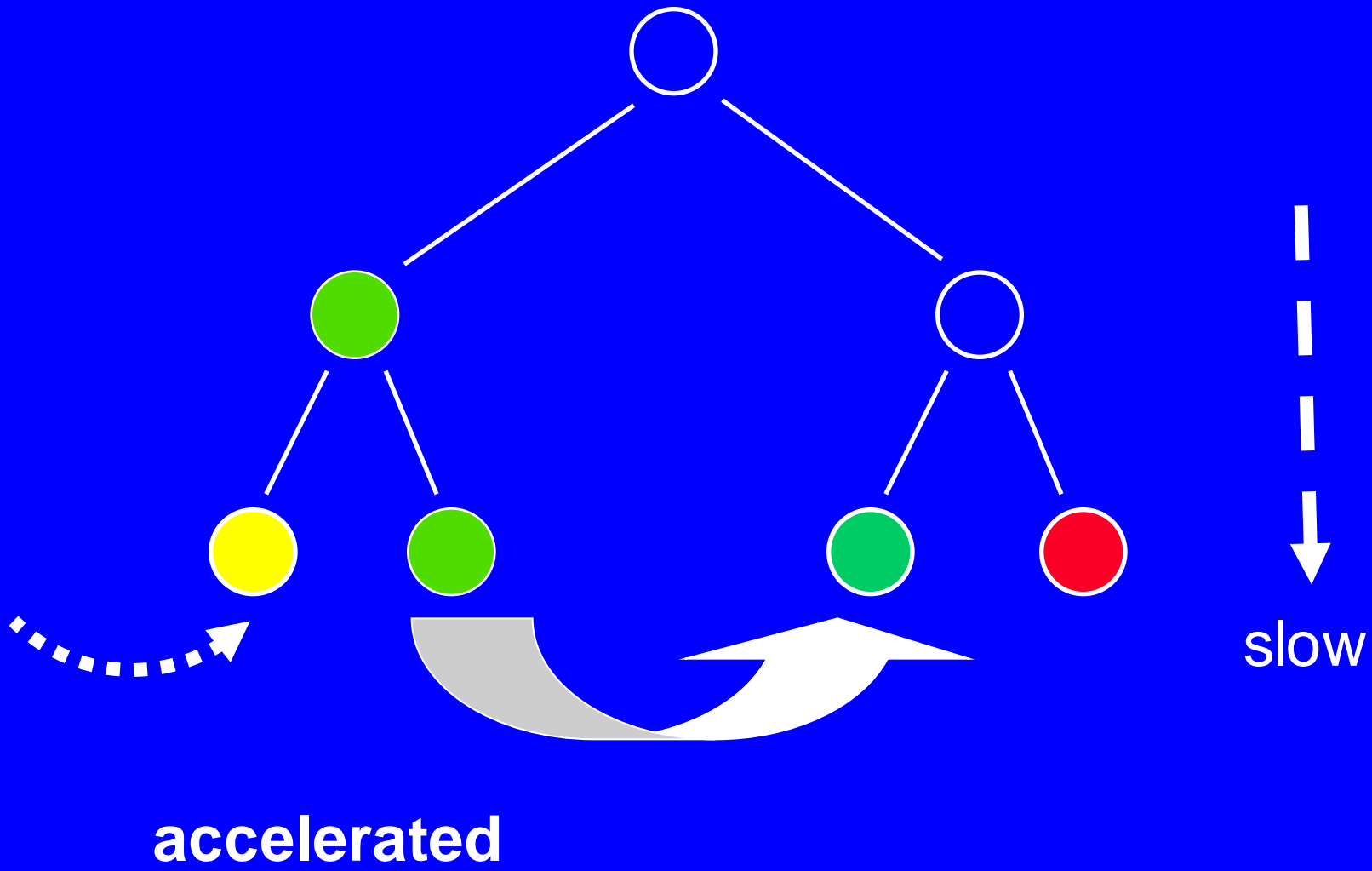




**Clonal population structure in which there is “vertical” descent with accumulation of variation through mutation and selection or drift.**

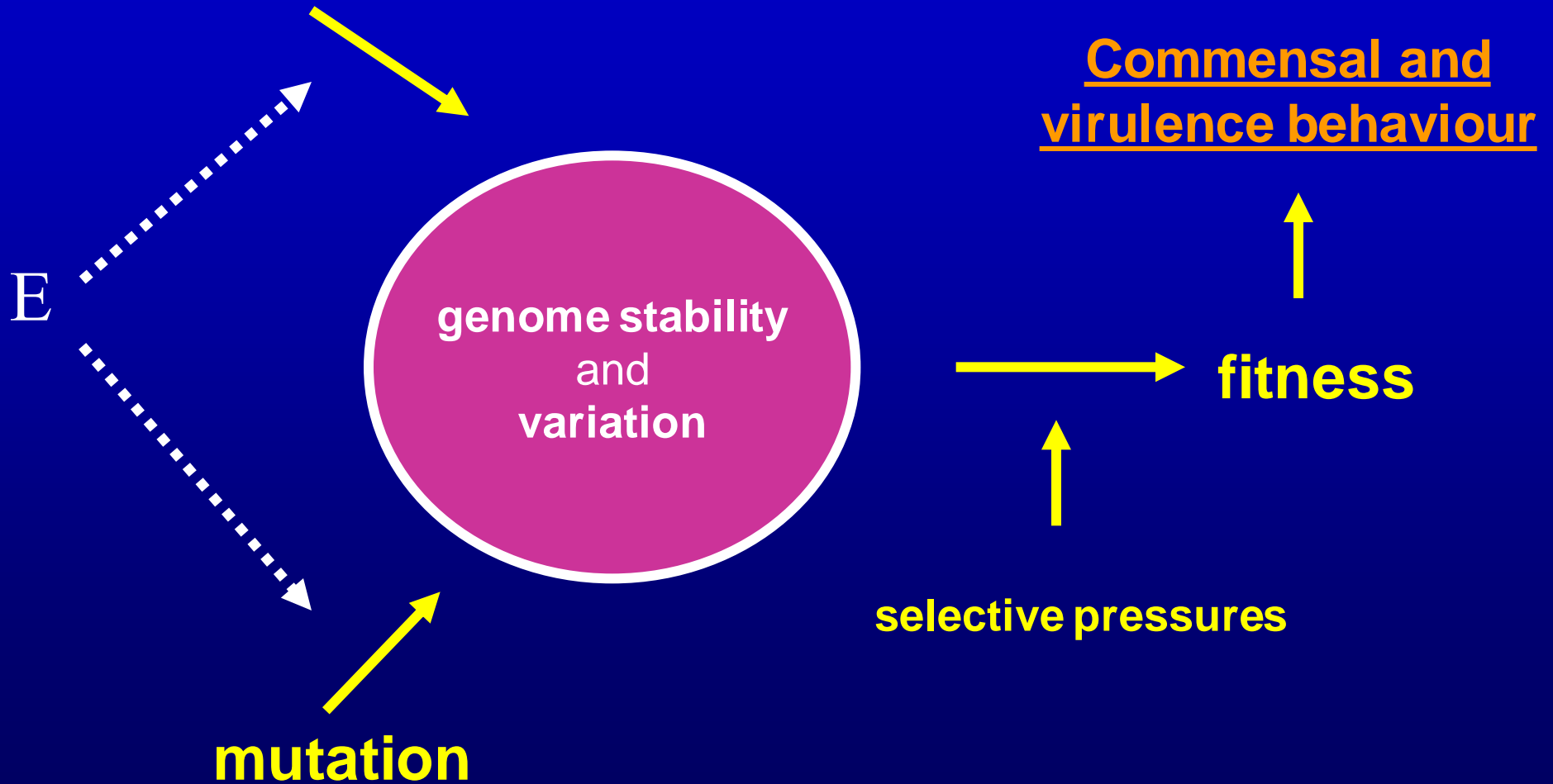


# Variations in sequence may arise through both vertical and horizontal genetic transfer



# genetic “intelligence”

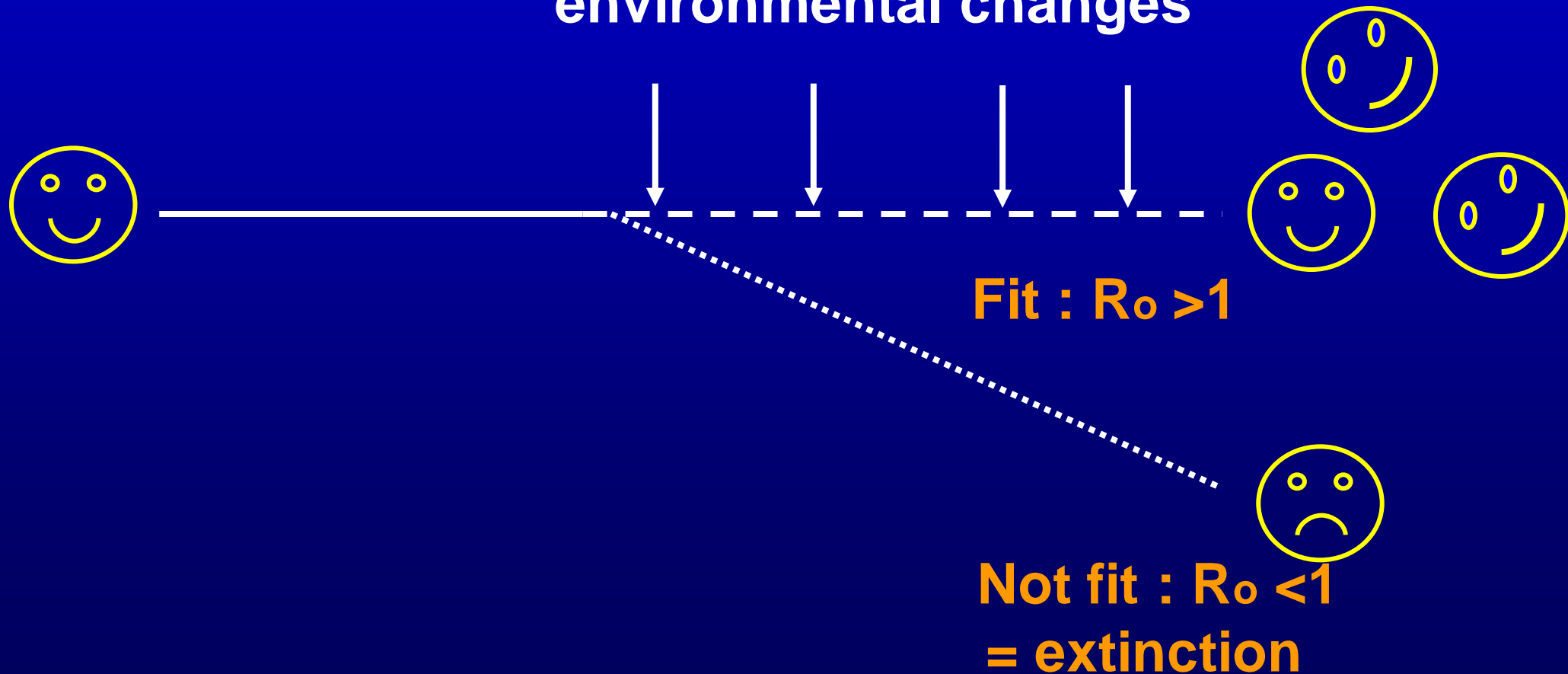
Genome maintenance



# Fitness

Basic reproductive rate ( $R_0$ )  $> 1$

environmental changes

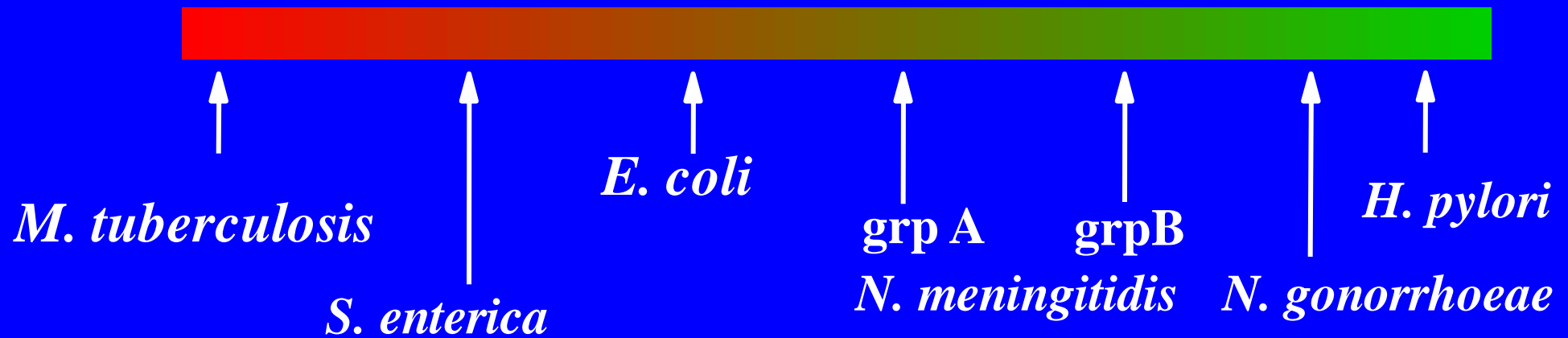


- **Large numbers**
- **Rapid replication**
- **Promiscuous exchange of genetic information**
- **Amount of recombination in bacteria dictates population structure**

# Bacteria exhibit a spectrum of population structures

clonal

non-clonal

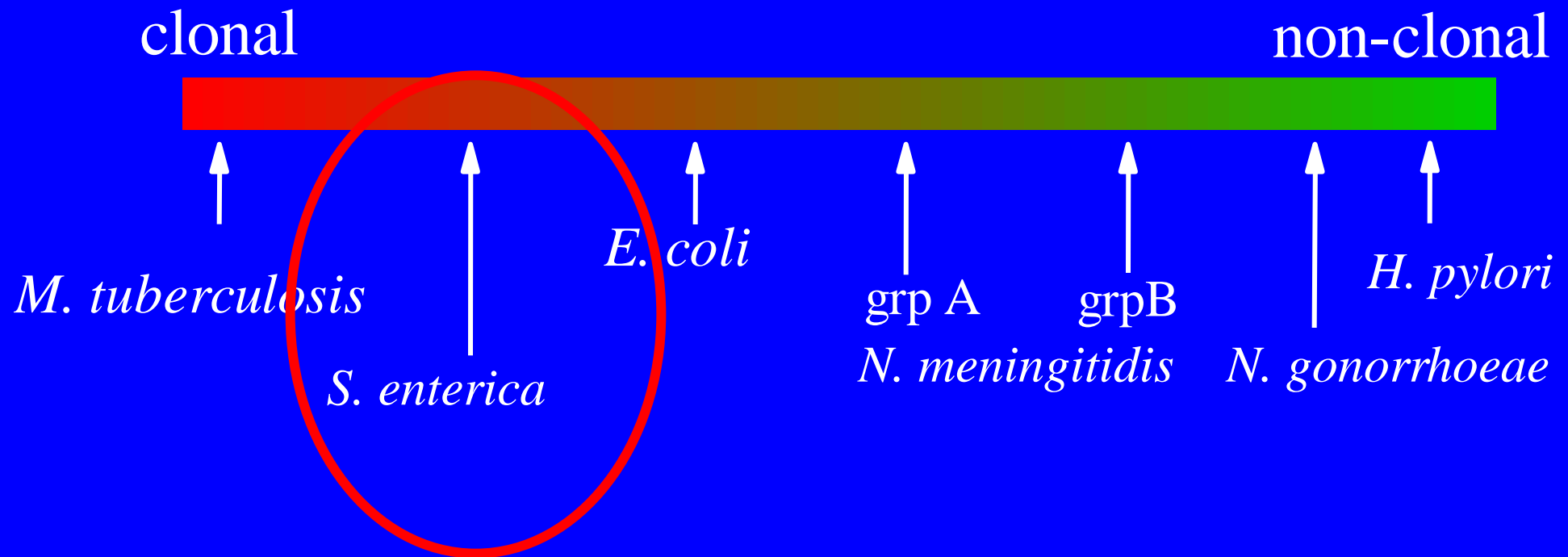


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# A spectrum of population structures

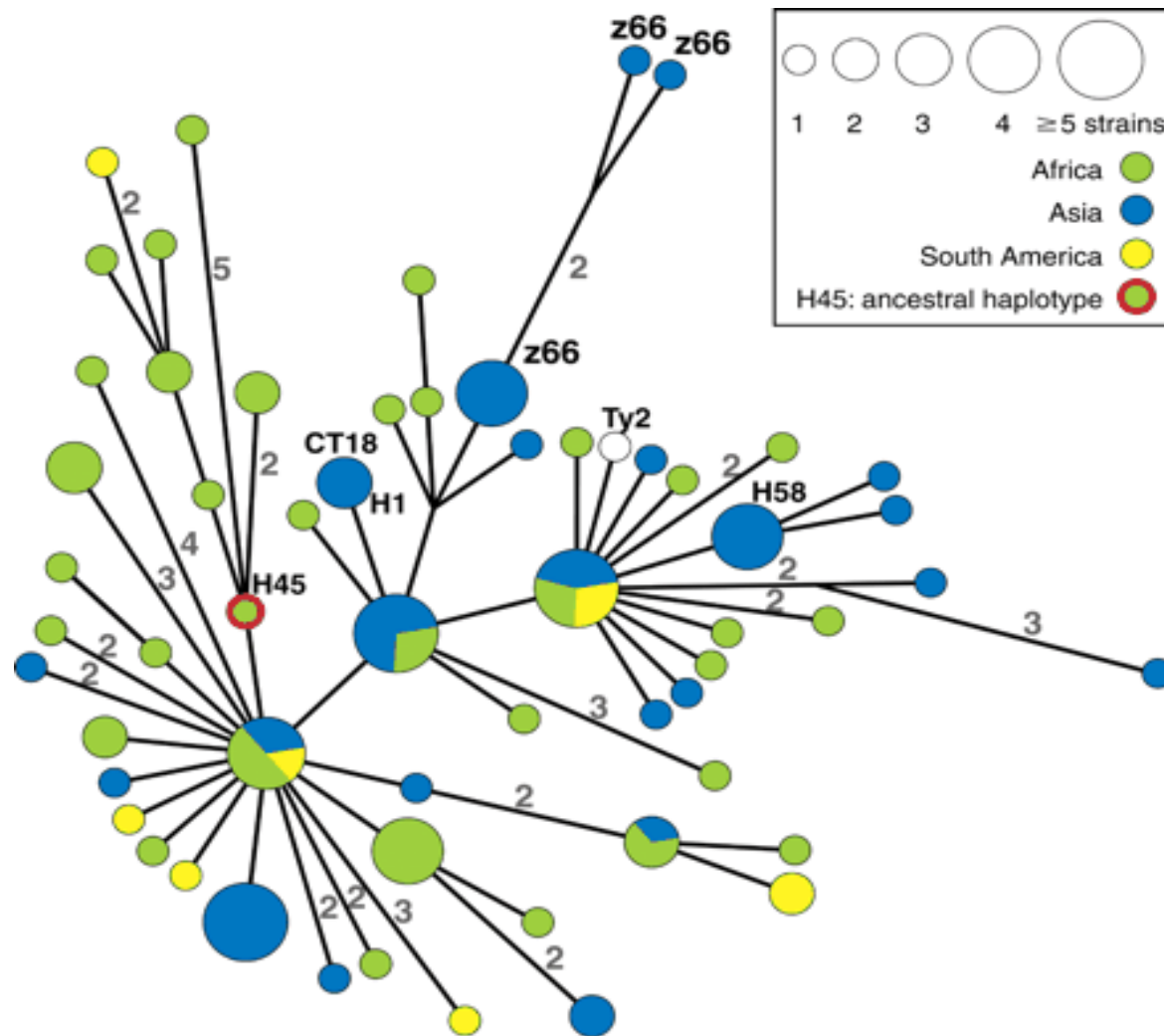




*Salmonella enterica* serovar *Typhi*

A clonal population structure: neutral evolution

# Detailed analysis of 105 serovar *Typhi* globally representative strains



Roumagnac *et al* 2006

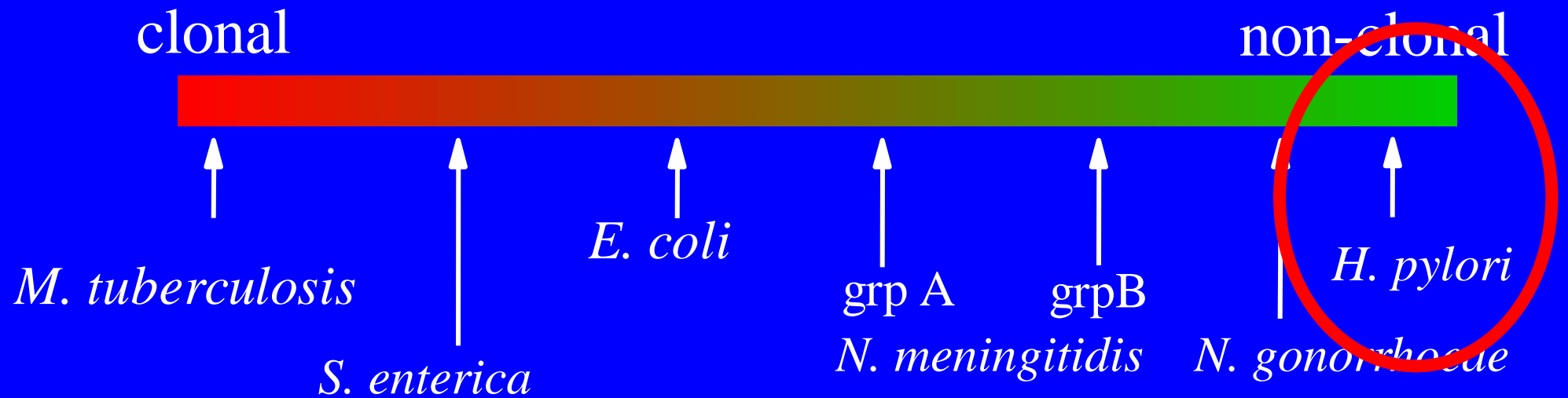
# *Salmonella enterica* serovar *Typhi*

**Example of neutral evolution – natural selection constrained**

**Multiple haplotypes (including ancestral H45 clones), globally distributed (obvious implications for target antigens for vaccines)**

**Population biology (neutral evolution) reflects the biology of carriage and transmission of *Typhi***

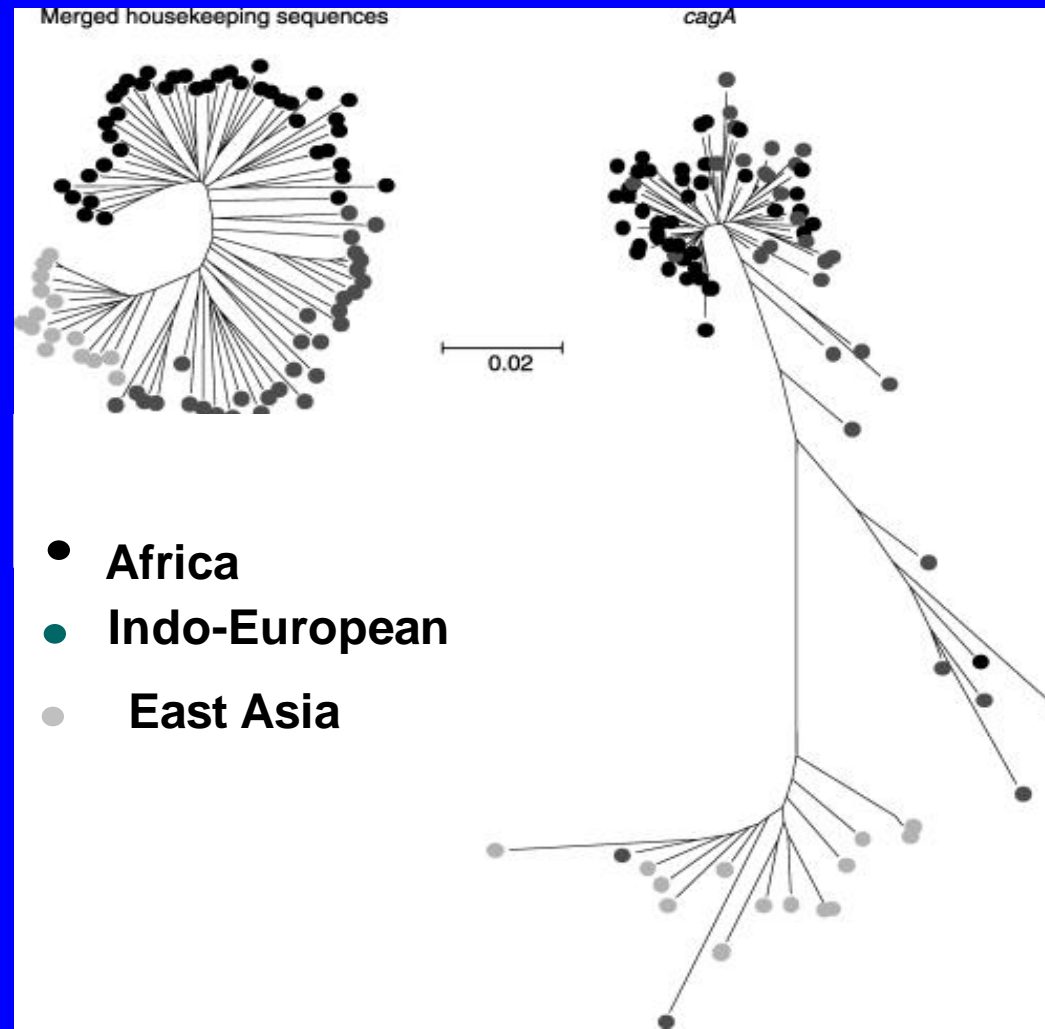
# A spectrum of population structures



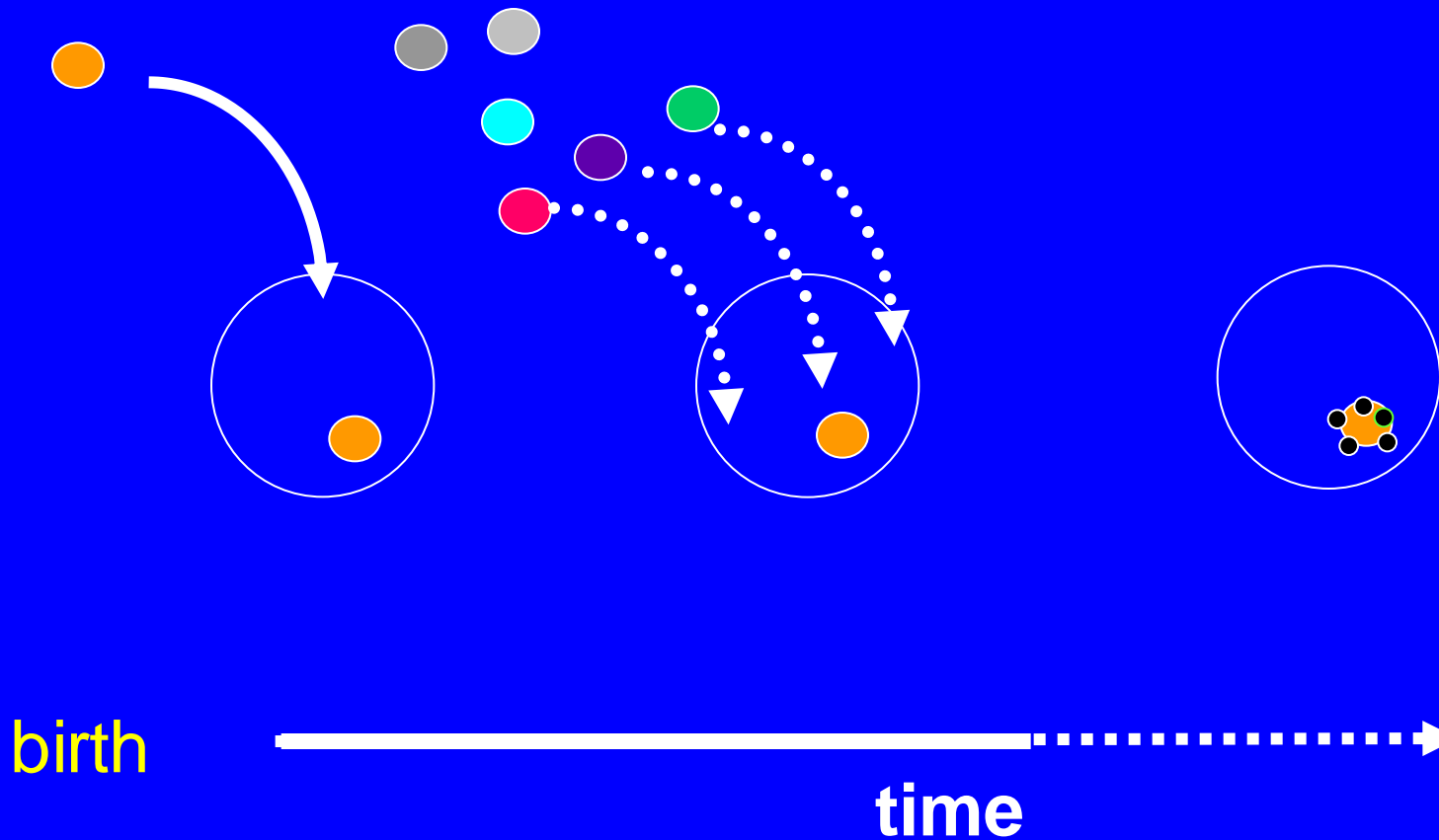
# *Helicobacter pylori*

A non-clonal population structure: lots of recombination and diversifying selection

# Non-concordance of a dispensable gene (CagA)



# Within host evolution of *H.pylori*



# Lessons from *Helicobacter pylori*

- **Strong geographical associations (informs about human migrations)**
- **Distinct clones are associated with humans over their entire life span. These long term “residents” acquire DNA from transient colonising strains.**
- **Gains and losses of DNA, intense selection generate huge diversity.**
- **Non-concordance between housekeeping and virulence genes – recombination: implications for vaccines**



# Outline of talk

## Part 1

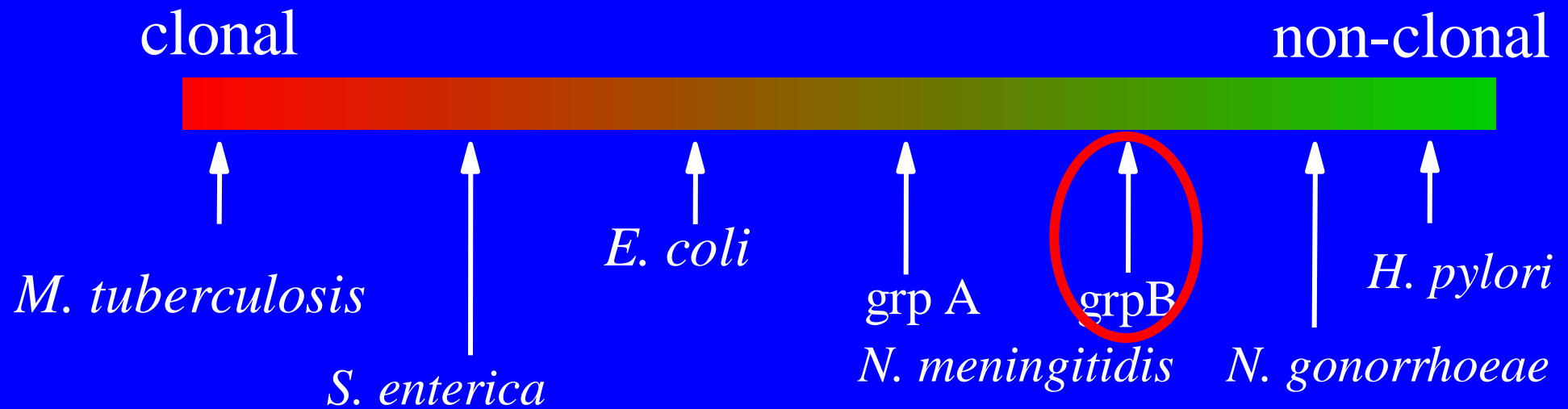
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# *Neisseria meningitidis*



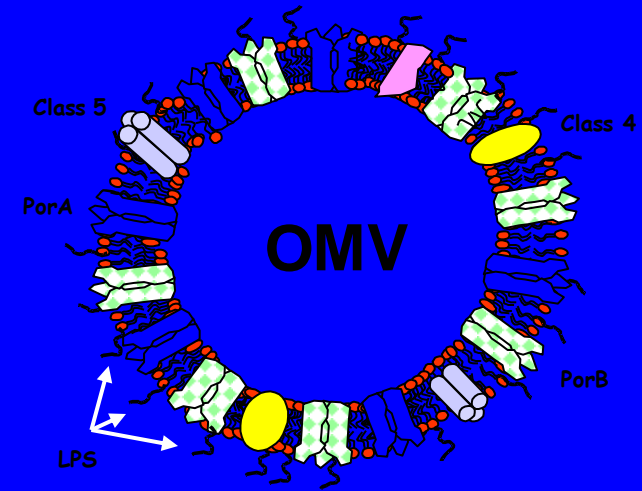
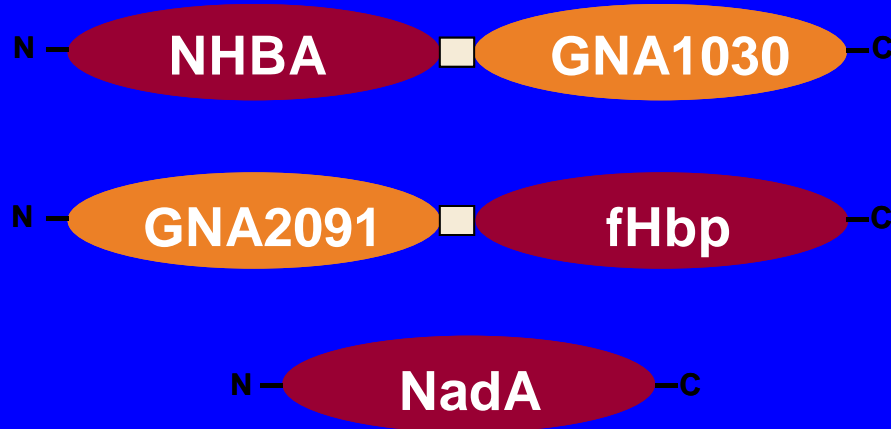
**The challenge of antigenic diversity**

# A spectrum of population structures



# 4CMenB Vaccine Composition

- Three protein antigens (two fusion proteins and one single polypeptide)
- Outer Membrane Vesicle (OMV) component (NZ PorA is P1.4)



Dose		OMV	Al <sup>3+</sup>	NHBA-1030	2091-fHbp	NadA
1	0.5ml	25 µg	0.5 mg	50 µg	50 µg	50 µg

# The challenge

**Variations in target (vaccine) antigens in the natural population *N. meningitidis* occurring over time and in different geographical settings**





































# Fundamentals

- ❑ Every meningococcal isolate has an antigenic profile (Vaccine Type)
- ❑ Serum bactericidal activity is a surrogate of protection

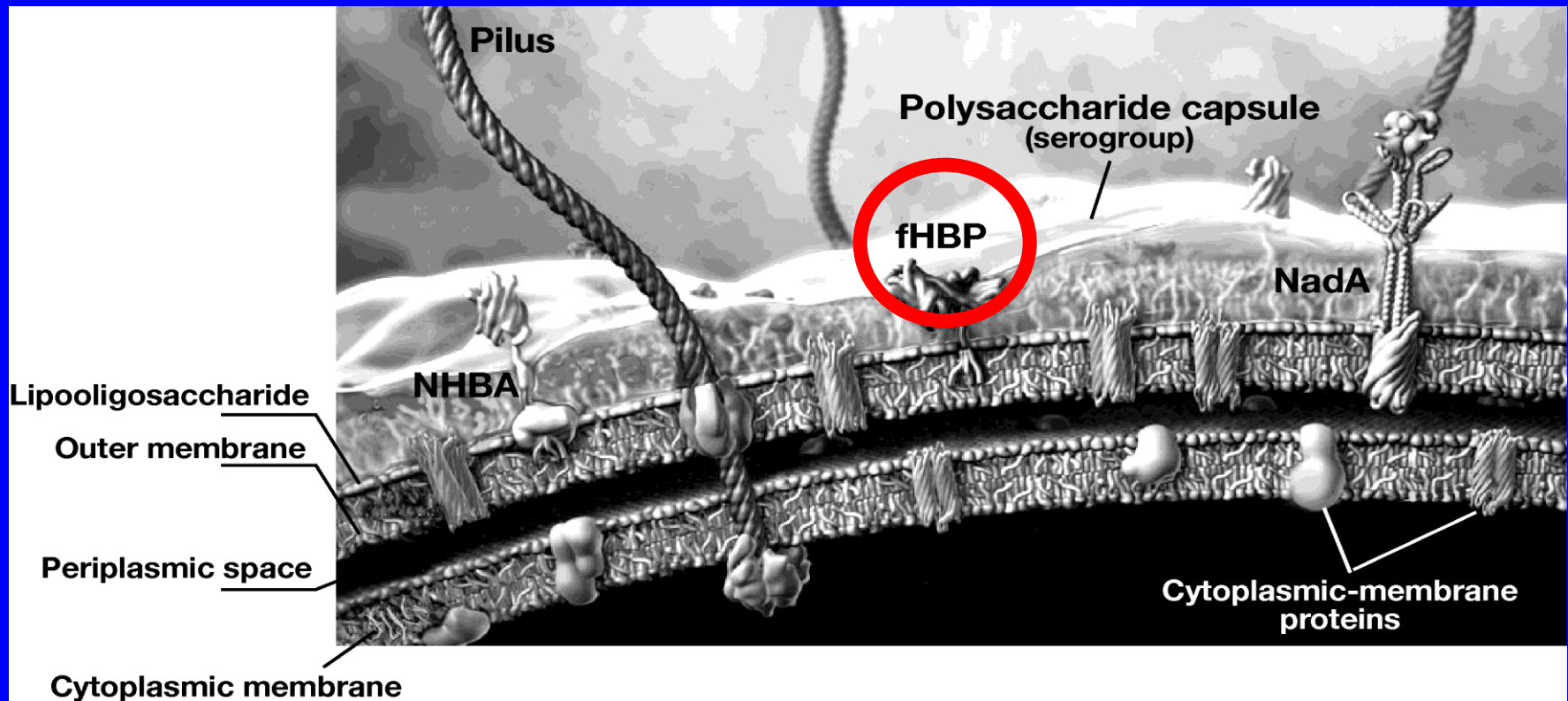
# vaccine type

# vaccine antigens

1	fHBP				
2	PorA				
3	NadA				
4	NHBA				
5	fHBP, PorA				
6	etc				
7					
8					
9					
10					
11					
12					
13					
14					
15					
16	NT				

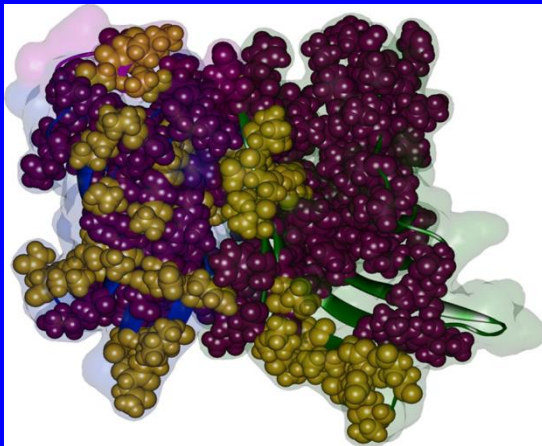
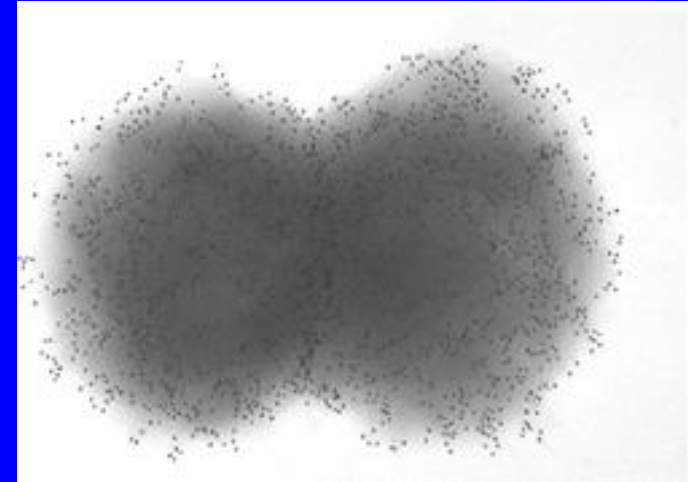


# Factor H Binding protein

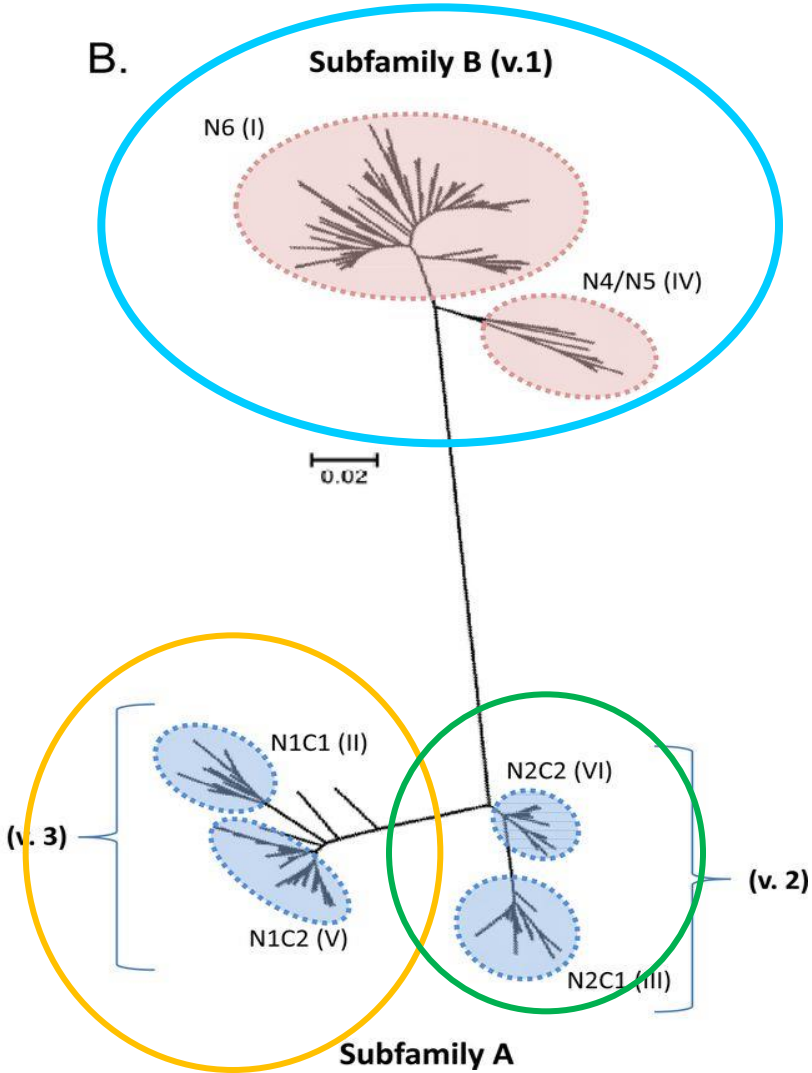


# fHbp - Factor H binding protein

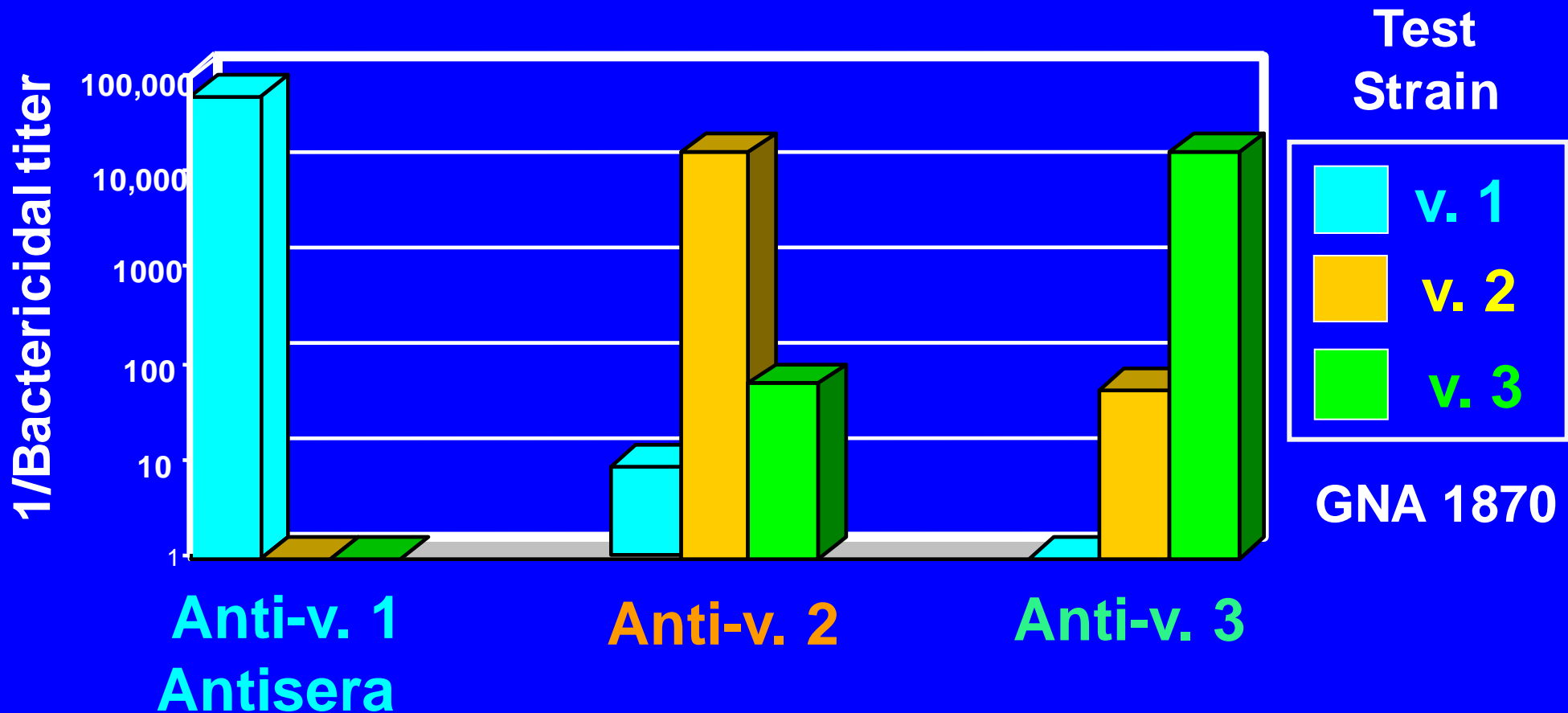
- fHbp is a 27-kDa surface-exposed lipoprotein of *N. meningitidis*
- *fHbp binds the human complement regulatory protein factor H (fH)*
- distinct variants identified based on variations in peptide (gold)



**Phylogenetic analysis of fHBP protein sequences.**



# Antigen B Bactericidal Antibody



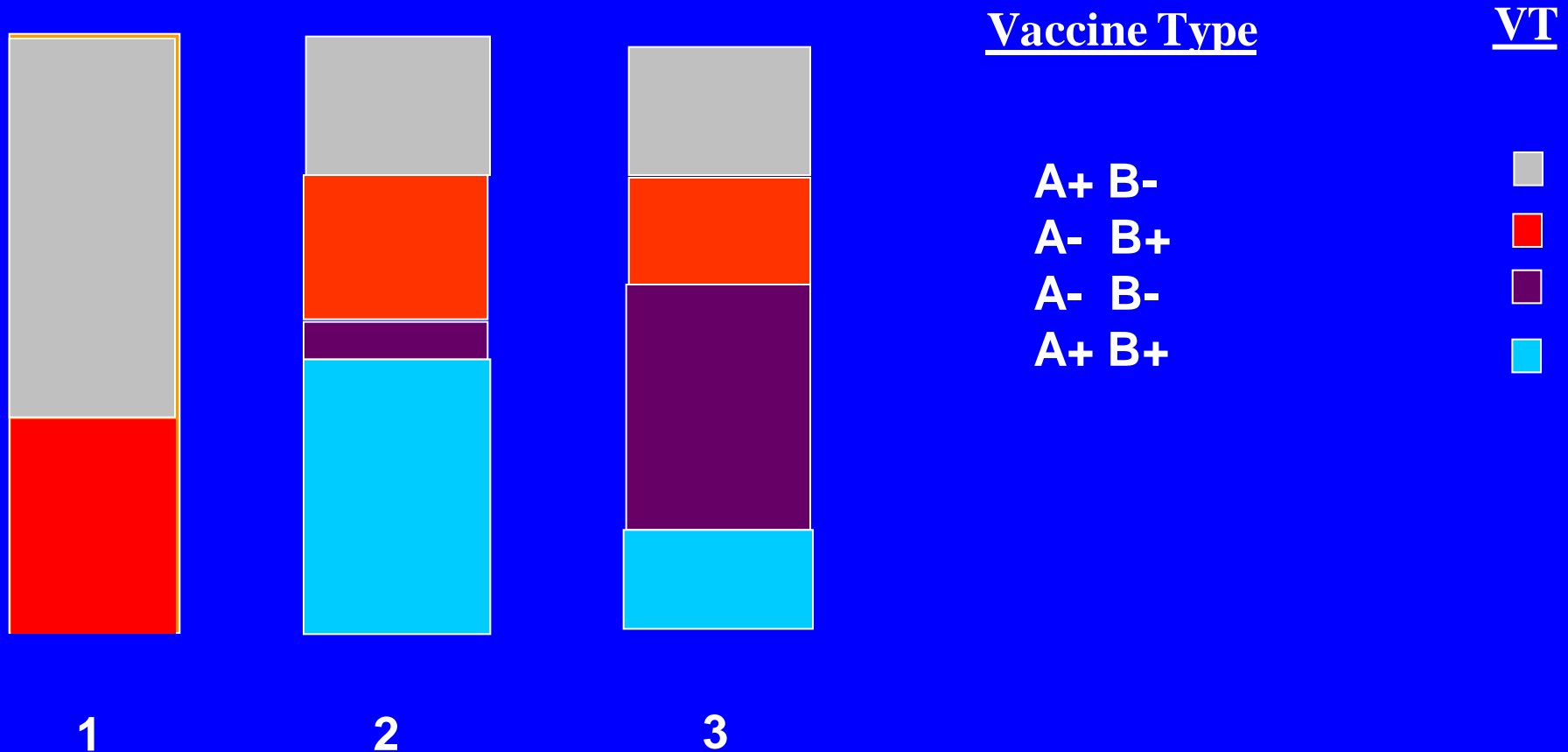
Massignani et al, J Exp Med 2003

# The challenge

**Variations in the natural population of the target organism occurring over time and in different geographical settings**

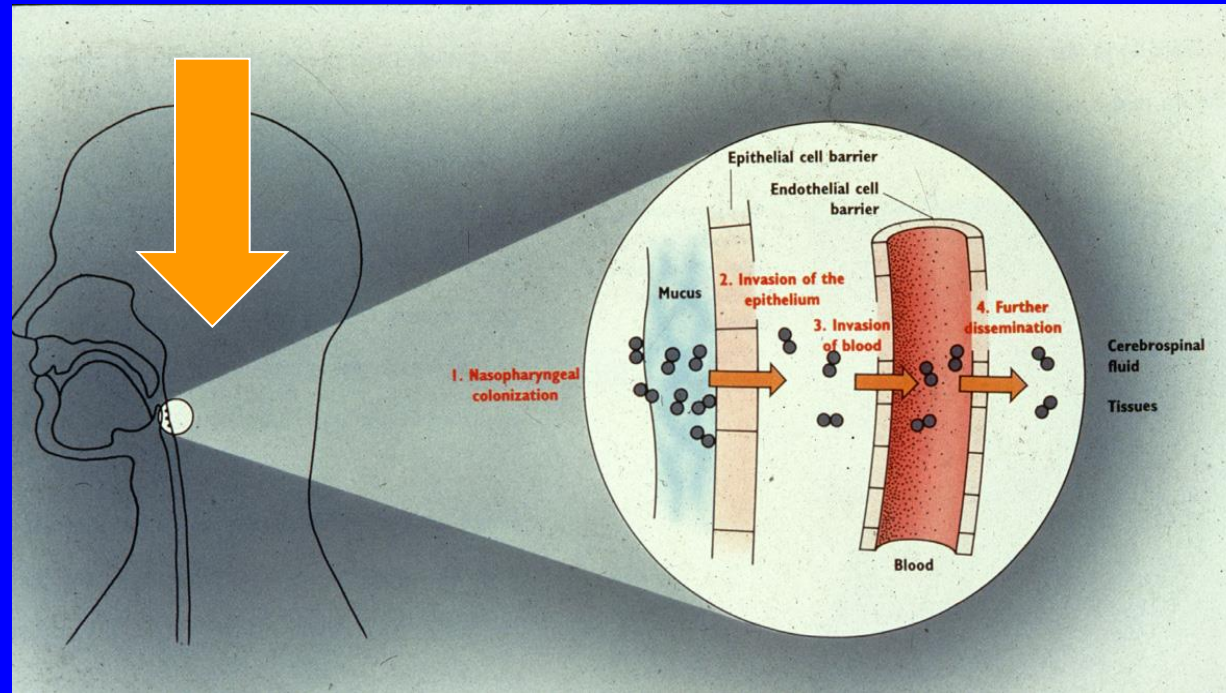
**How will 4CMenB perform -- in each country as a whole and considering regional and temporal variations?**

# Indexing Vaccine Type prevalence in different geographical regions or temporal variation in order to estimate potential vaccine coverage



# Direct and indirect protection

# Vaccines against commensal pathogens



**Where do host immune responses exert their selective effects on meningococci?**



**The major factor driving the diversity within natural populations of *N. meningitidis* is the capacity to survive within and spread between human respiratory tracts**

**For many commensal pathogens, such as the meningococcus, invasive disease is incidental (accidental?) to their evolution and fitness to survive**

# **The new era of meningococcal vaccines**

- **The biological rationale for Nm vaccines changes**
- **It is no longer a capsule (serogroup) “world”!**
- **Diversity of protein vaccine antigens is a major challenge**

# Some conclusions -1

- 1. Using population biology to index diversity of organisms and specific antigens, judicious selection of components of a vaccine can be achieved that maximise coverage**
- 2. This information needs to take in account evolutionary changes (time and geography) within the natural population of bacterial pathogens**

## Some conclusions - 2

- 3. Although present on the bacterial cell surface, the conformation and amount of an antigen may vary from strain to strain**
- 4. Must take into account individual variations in host immune responses to vaccine antigens.**

## Some conclusions - 3

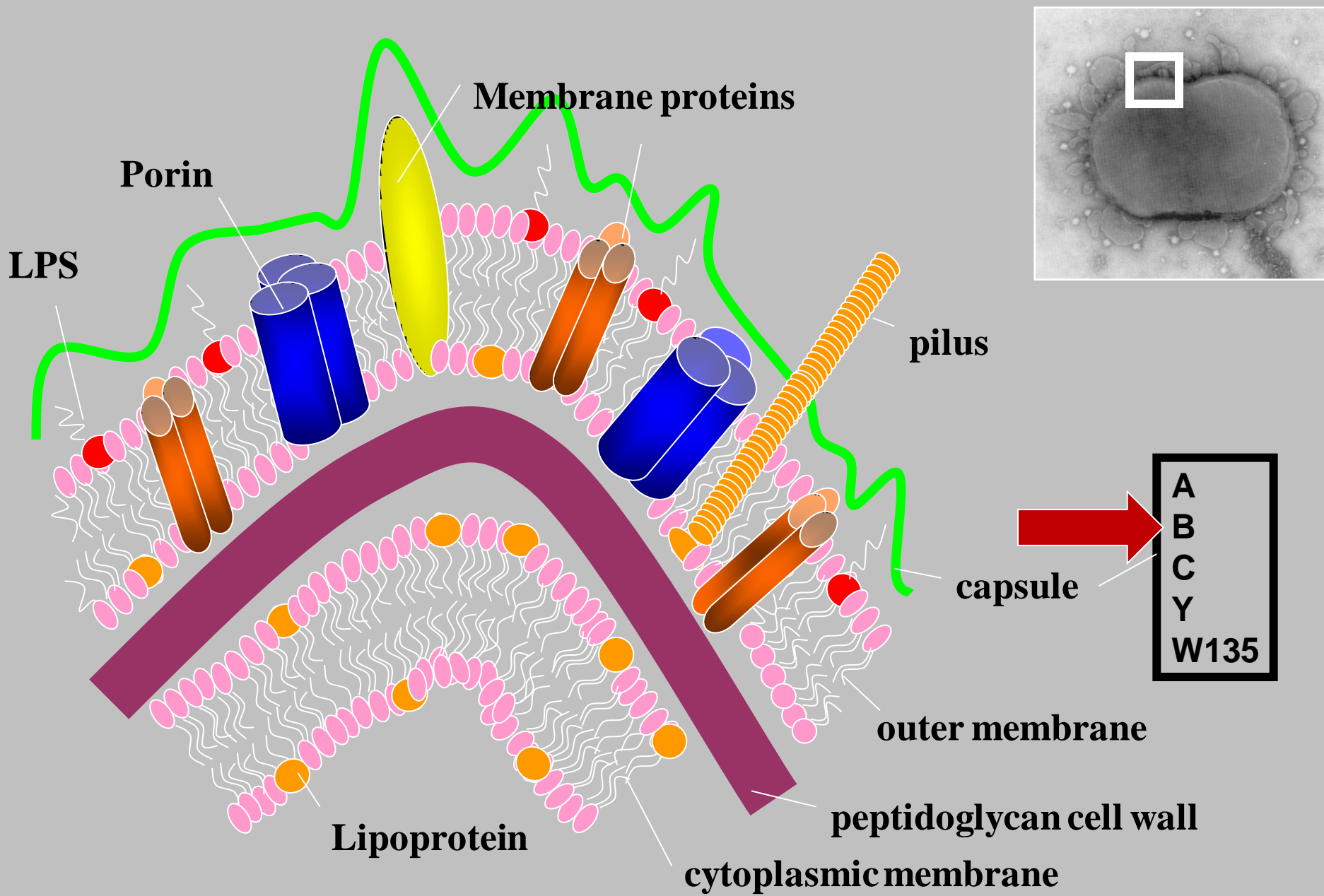
5. **If vaccine decreases carriage through reduced transmission, disease decreases.**
6. **A two edged sword? (e.g. serotype replacement)**
7. **Elimination of vaccine strains may alter ecology and facilitate replacement with other strains that are not susceptible to the vaccine**





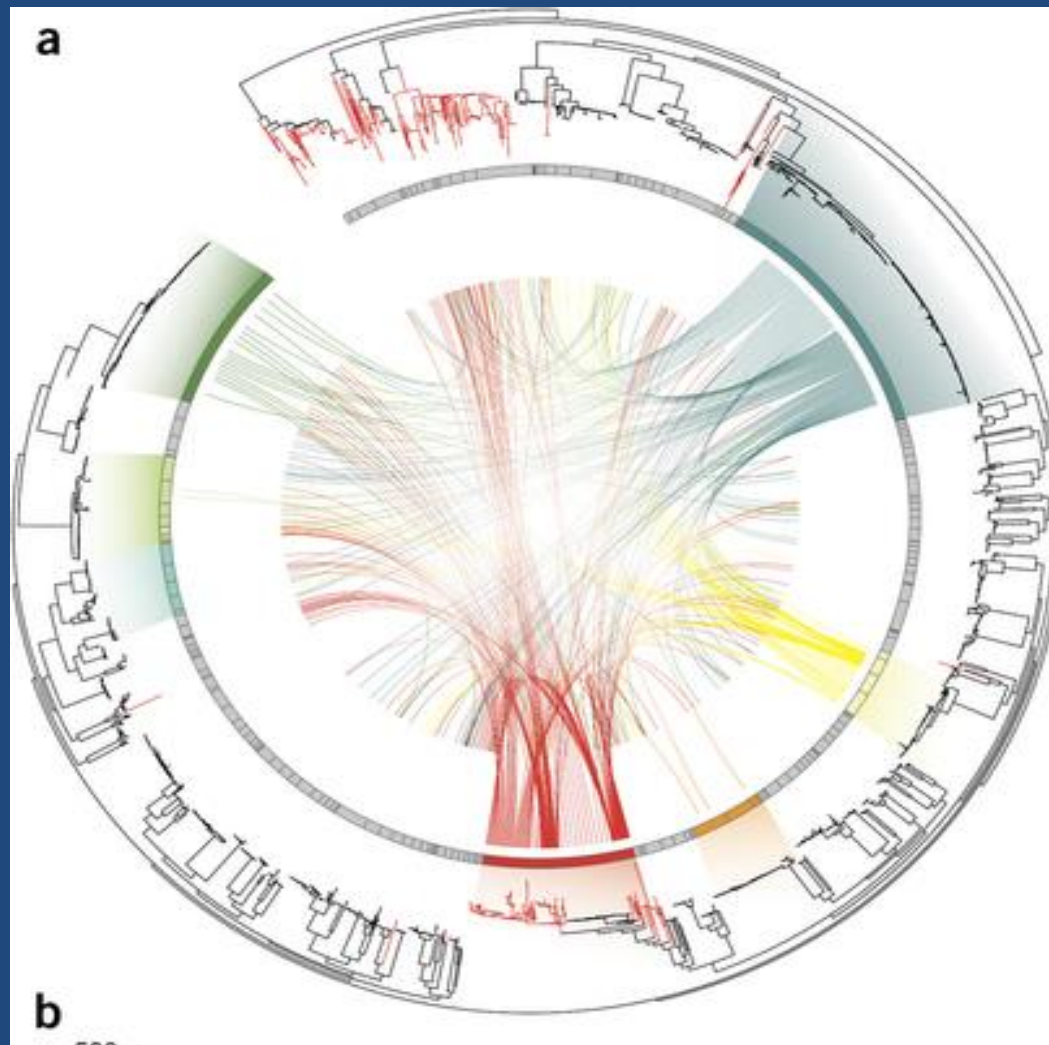
**Back up slides**

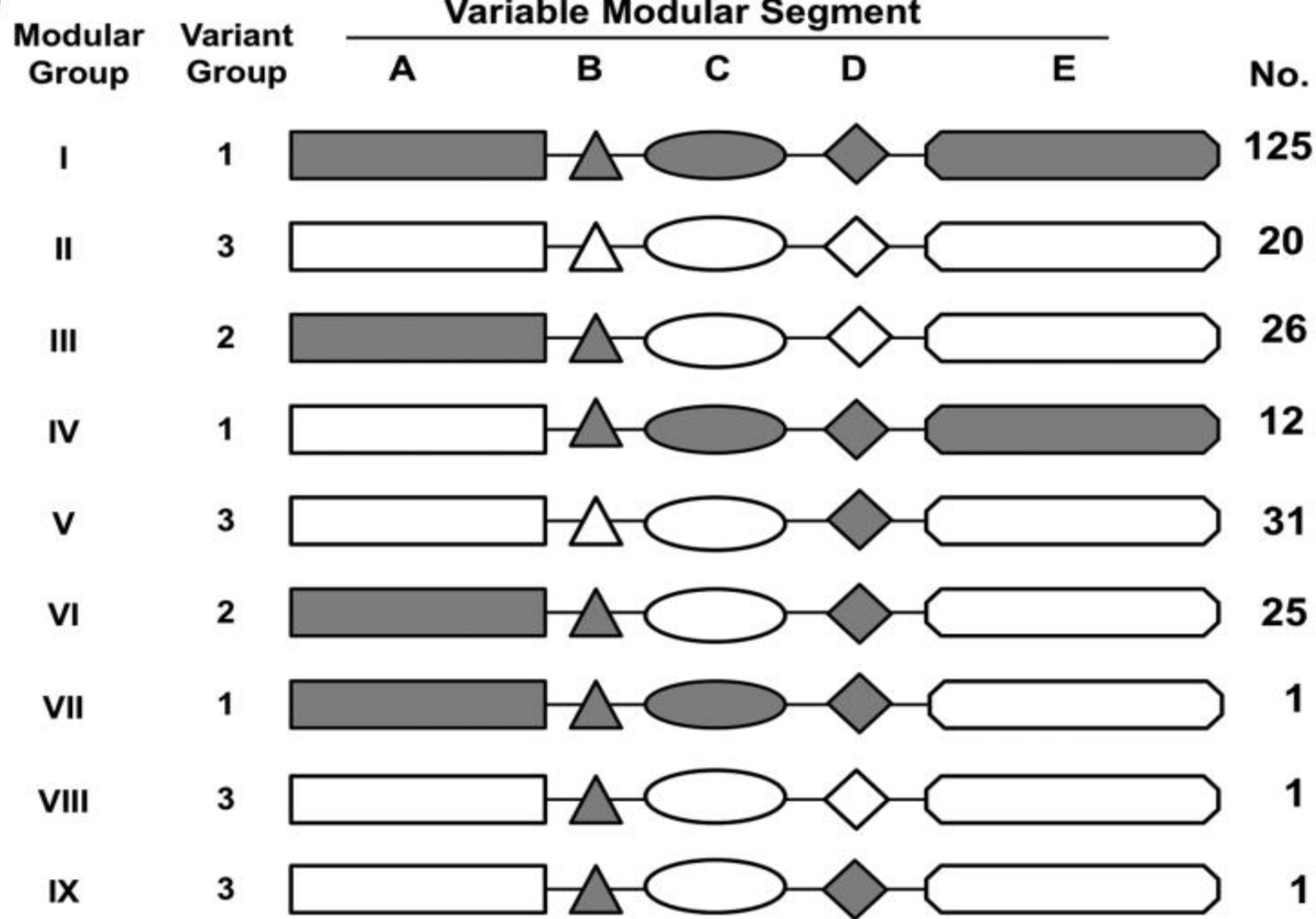




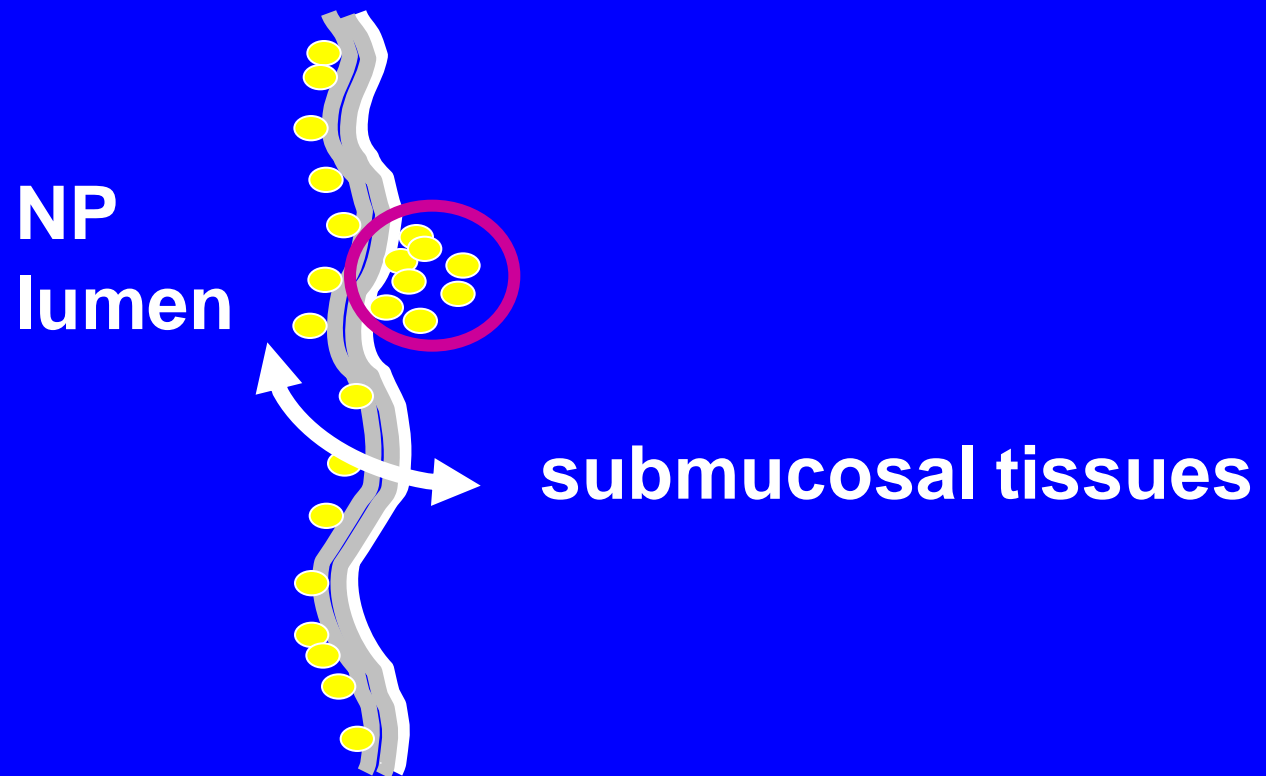
# Dense genomic sampling identifies highways of pneumococcal recombination

Nature Genetics 2014. Cheewapreecha et al

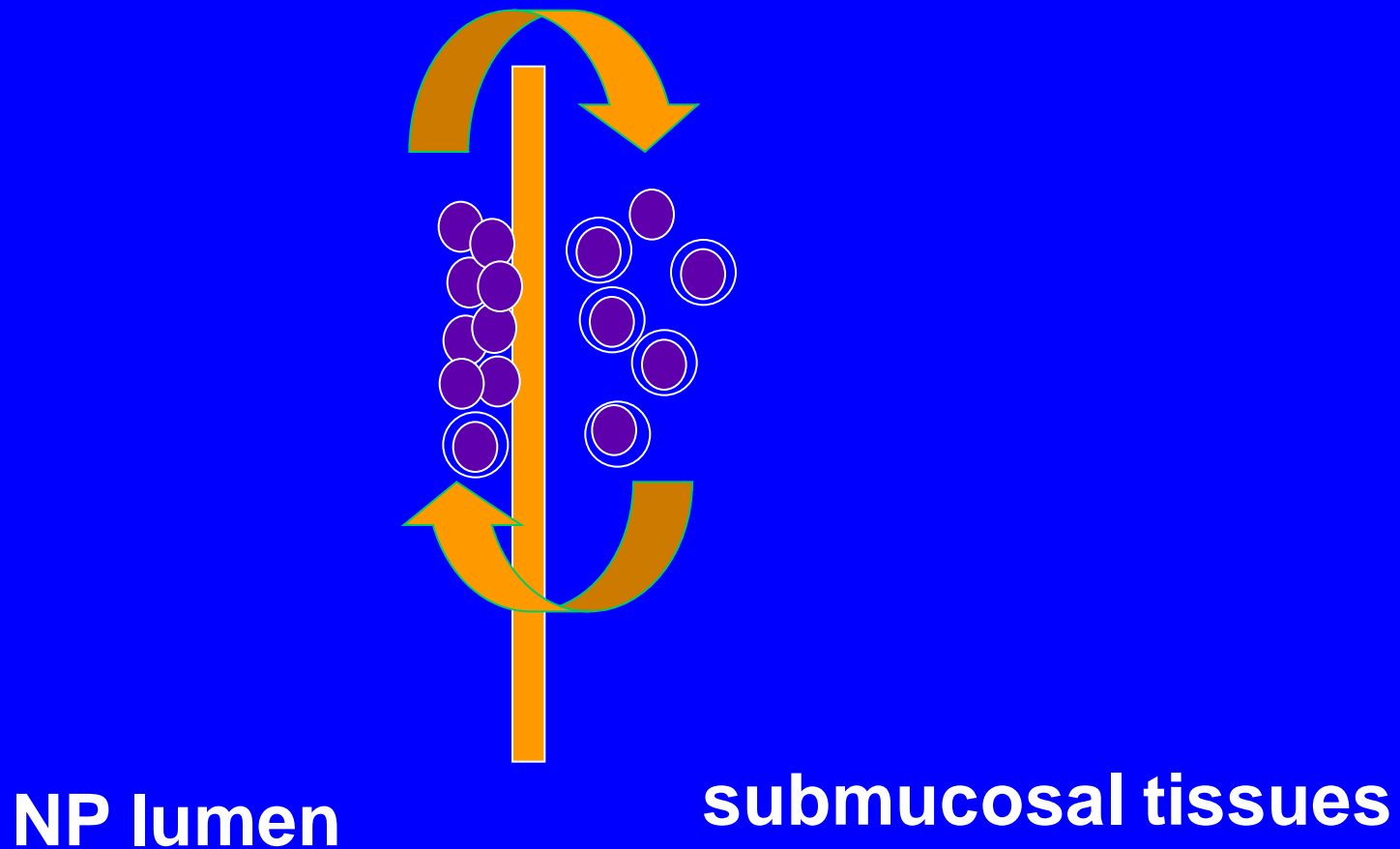




# Where do meningococci reside in the human nasopharynx?



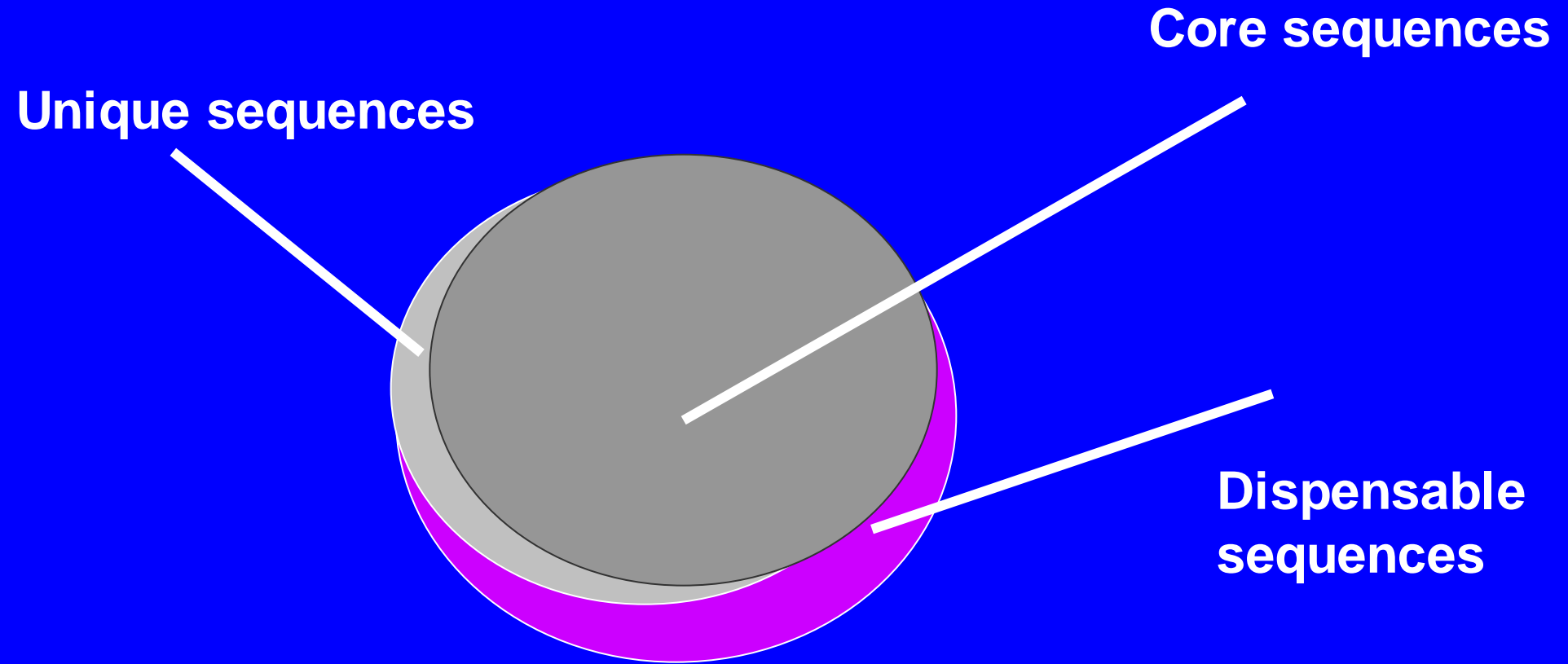
# Dynamic transition between lumen and submucosa selects for antigenic variation



# Fundamentals

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# Concept of species pangenome

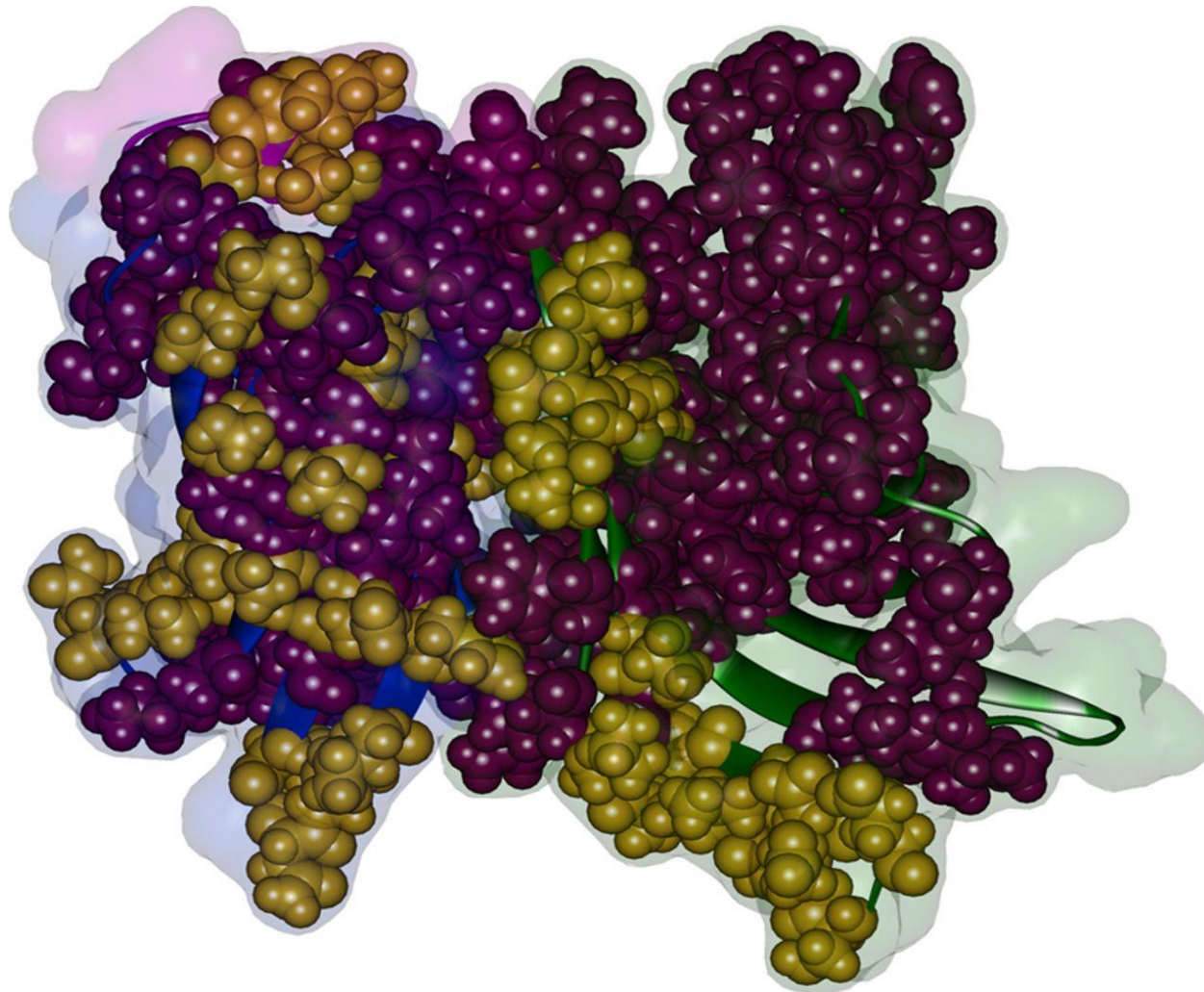


# **“Bet- hedging”**

- **All microbes face the challenge of out-competing their hosts and other factors (e.g indigenous flora)**
- **Antigenic variation (allelic diversity, phase variation and other forms of molecular switching) are evolved strategies that facilitate the fitness of microbes**



**fHBP conservation within and across the A and B subfamilies.**



McNeil L K et al. *Microbiol. Mol. Biol. Rev.* 2013;77:234-252

Microbiology and Molecular Biology Reviews

**‘Balloon’ representation of *N.meningitidis* clones to depict non-concordance between genotype (colours) and fHBP (sequence space)**

