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Reverse Vaccinology

A new way to develop vaccines

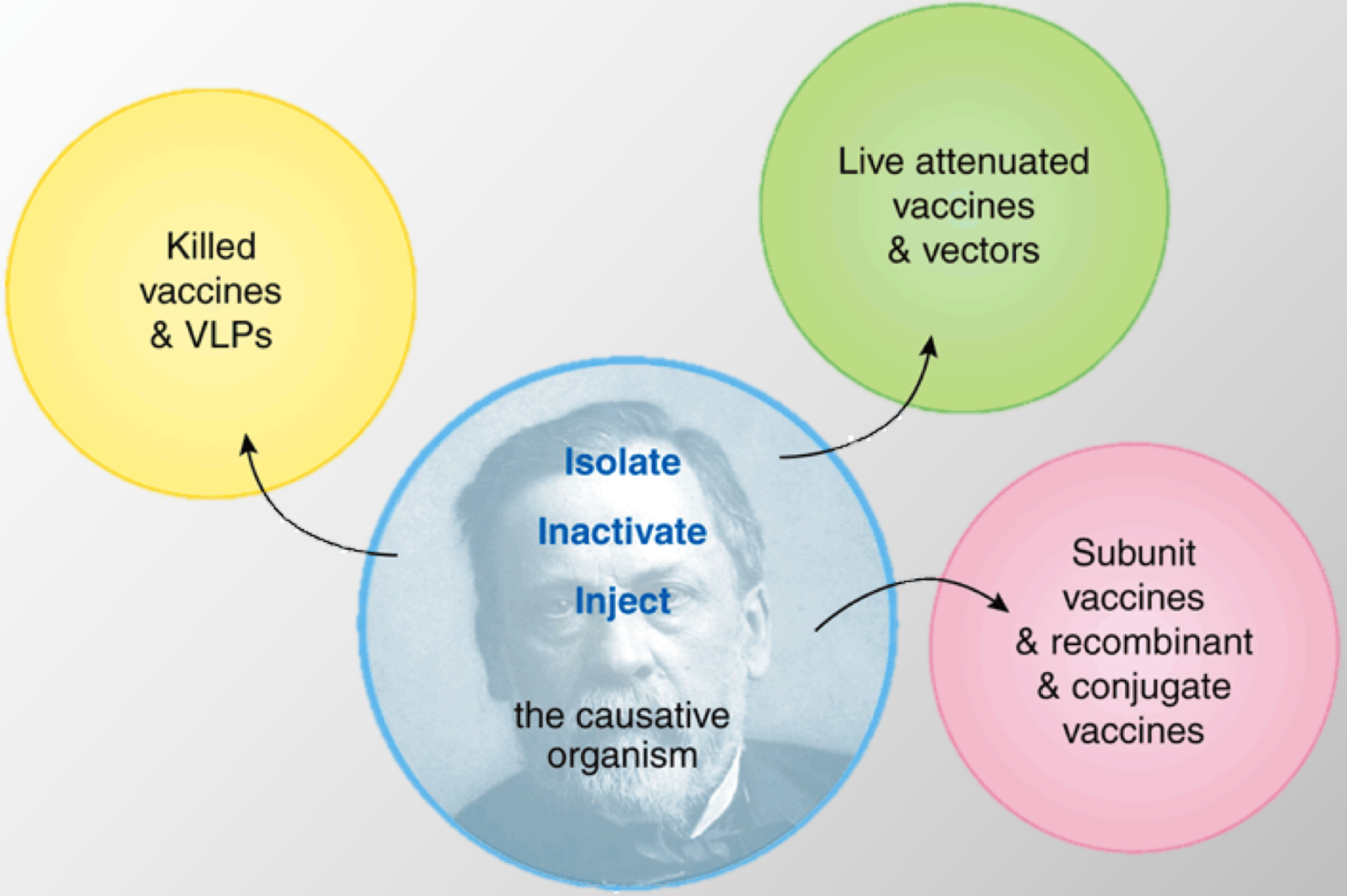
Chiara Faso et Francesco Rioli

Referente: Prof. Pinti

Outline of the talk

- Characteristics and limits of conventional vaccinology
- Creation of a new approach which starts from the microorganism genome
- Application of the method to *N. meningitidis*

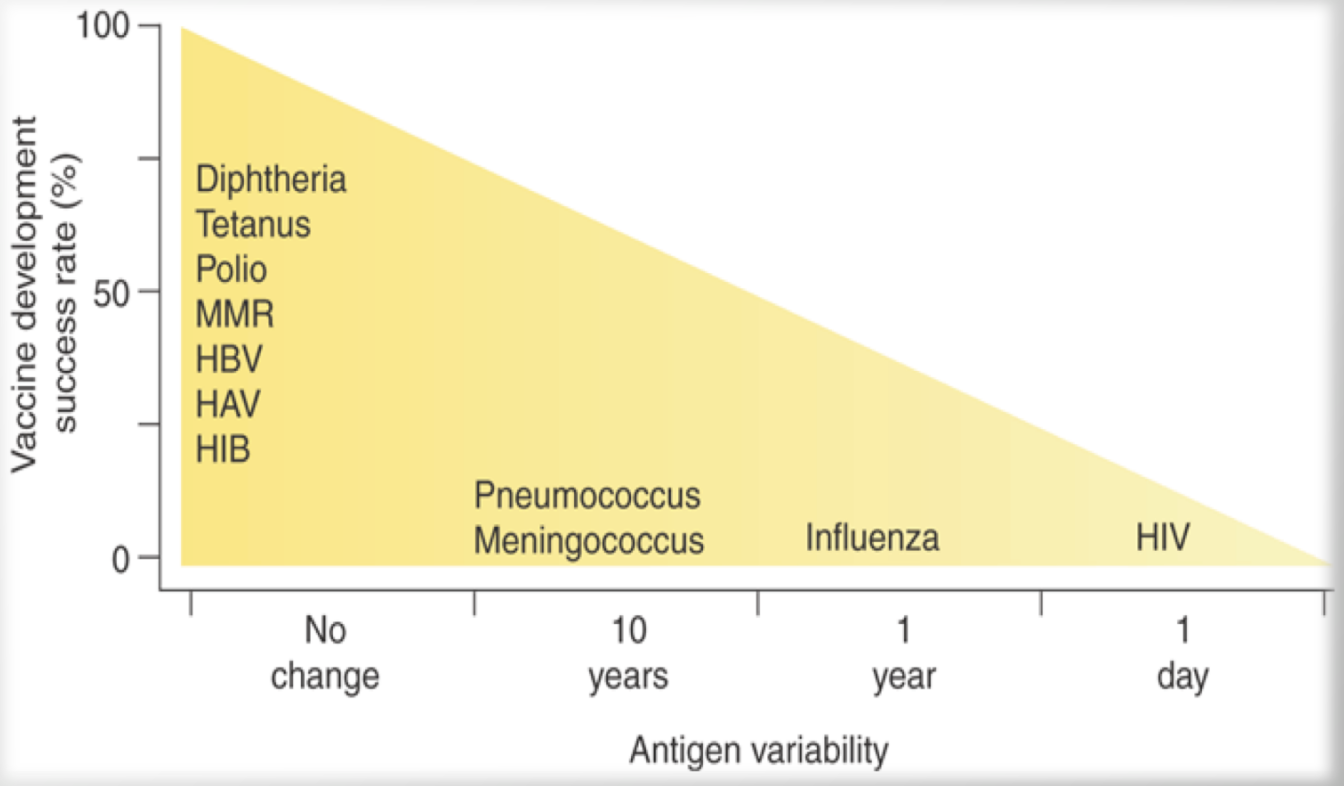
Conventional vaccinology



[1]

LIMITS of conventional approach

- Timing (10 y)
- Cultivable
- Few Ags
- Ags only expressed *in vitro*
- Antigenic variability



[2]

REVERSING THE PARADIGM

Reverse vaccinology

Rino Rappuoli

Biochemical, serological and microbiological methods have been used to dissect pathogens and identify the components useful for vaccine development. Although successful in many cases, this approach is time-consuming and fails when the pathogens cannot be cultivated *in vitro*, or when the most abundant antigens are variable in sequence. Now genomic approaches allow prediction of all antigens, independent of their abundance and immunogenicity during infection, without the need to grow the pathogen *in vitro*. This allows vaccine development using non-conventional antigens and exploiting non-conventional arms of the immune system. Many vaccines impossible to develop so far will become a reality. Since the process of vaccine discovery starts in silico using the genetic information rather than the pathogen itself, this novel process can be named reverse vaccinology.

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Current Opinion in Microbiology 2000, **3**:445–450

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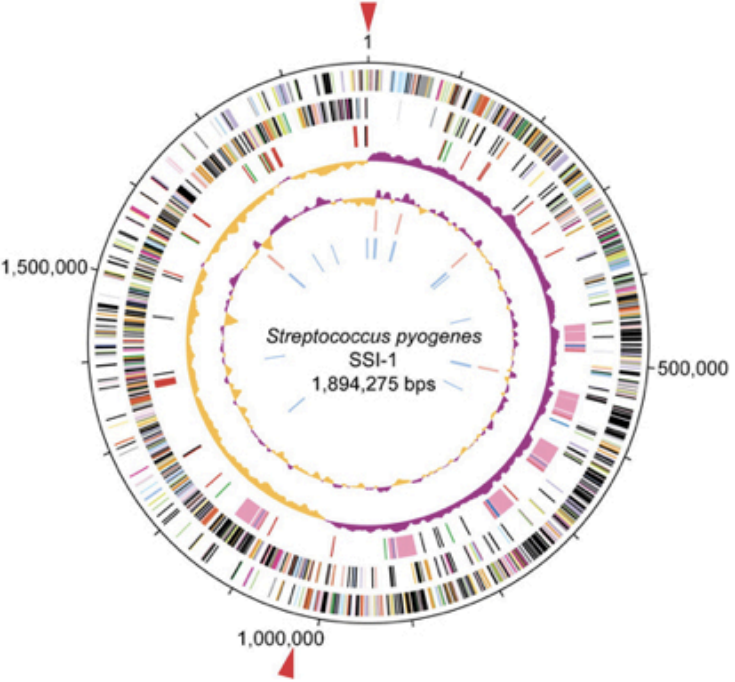
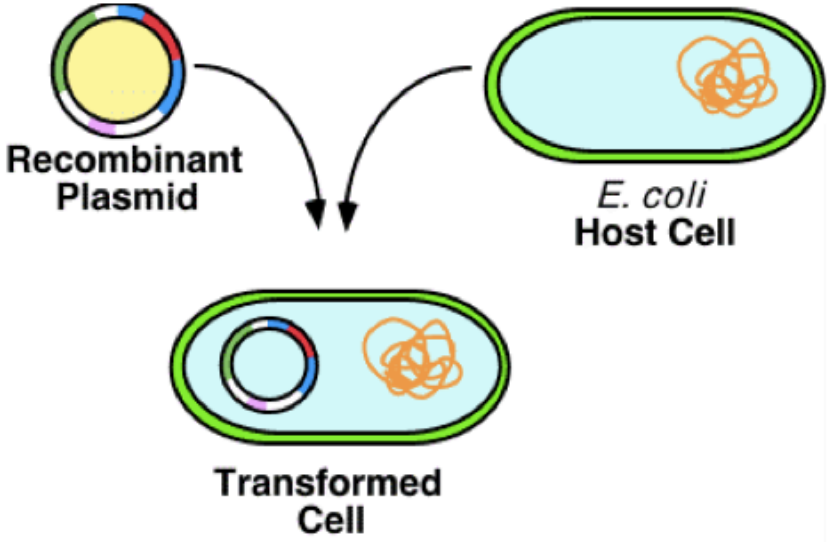
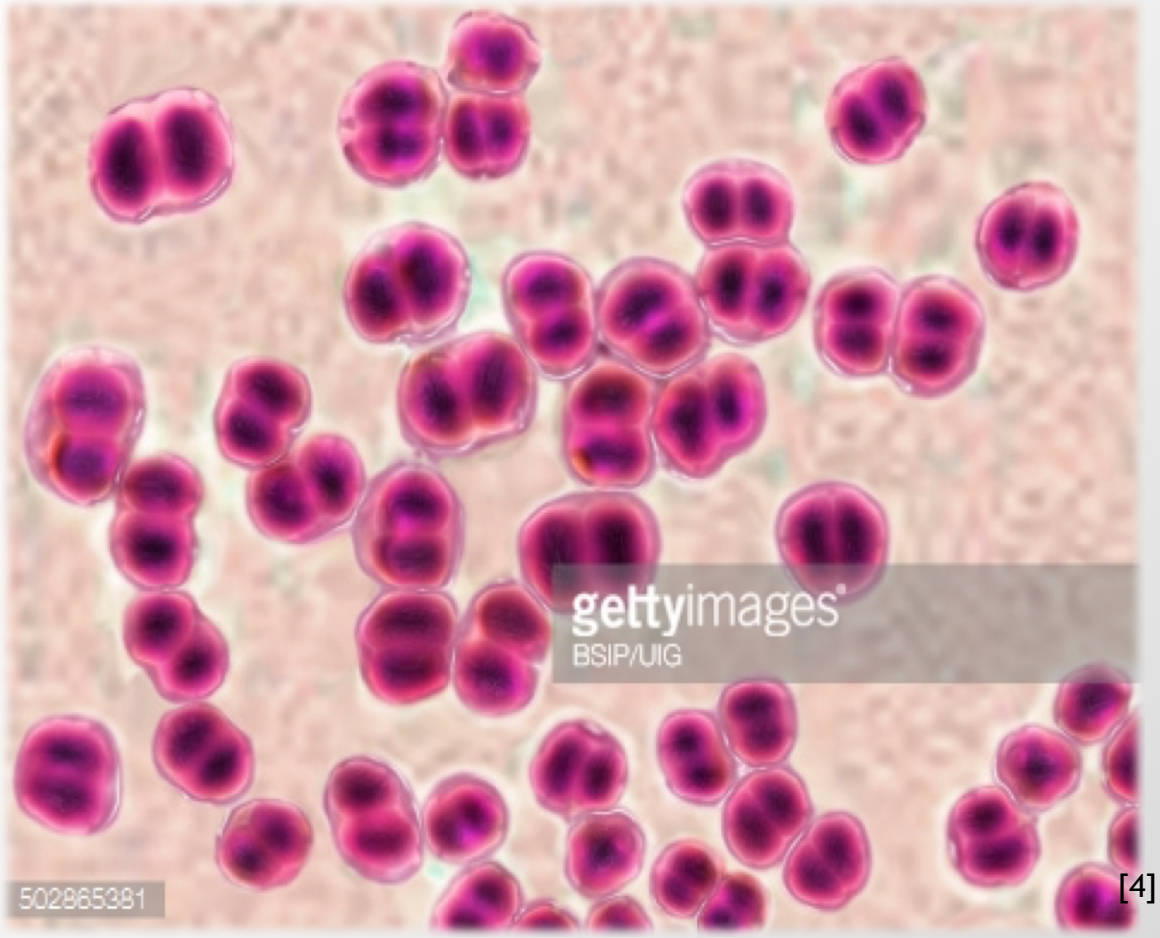


Identify potential ORFs by bioinformatics: GENE-PROTEIN correlation



Evalution of serum Ab titre & correlates of protection assay

Application of the method: *N. meningitidis*



[4]

Gram- capsulated bacteria

One of the causative organism of septic MENINGITIS

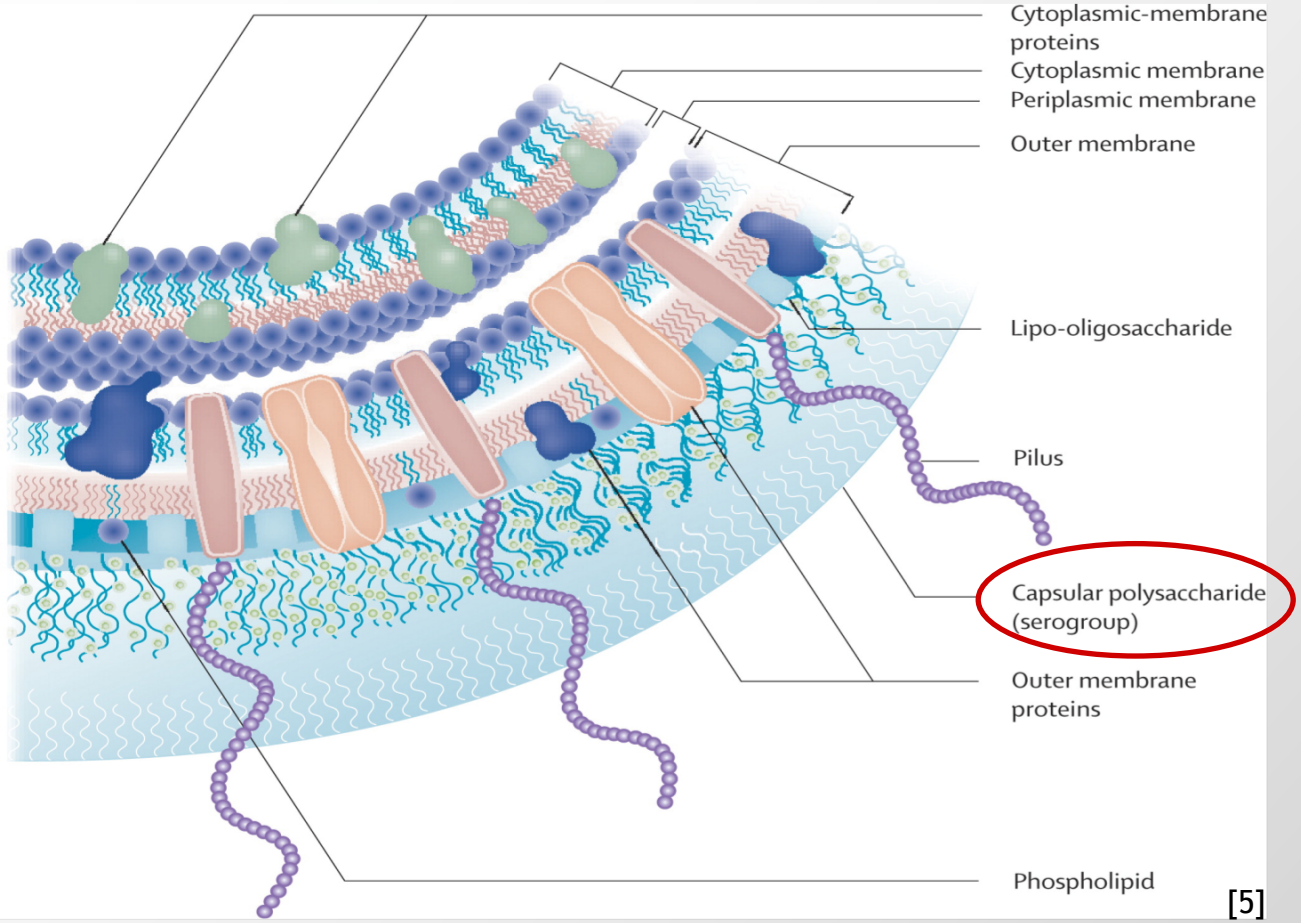
13 CAPSULAR SEROTYPES, 5 of them are mostly responsible for the disease:

A, B , C, Y, W135 (X)

1 – MenB capsular antigen-based vaccine

Poorly immunogenic

Potential cause of autoimmunity



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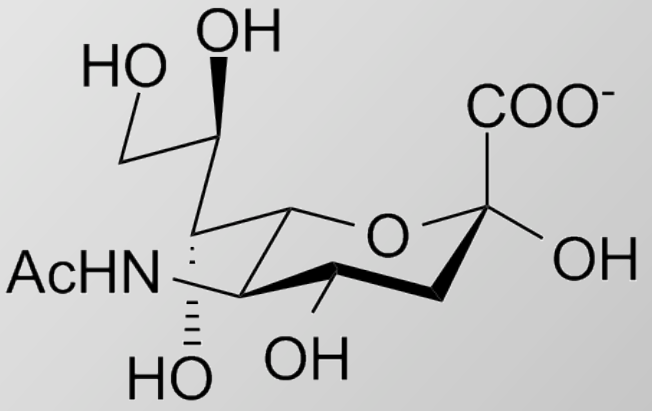


Alfa(2→8) N-acetyl neuraminic acid (polysialic acid)

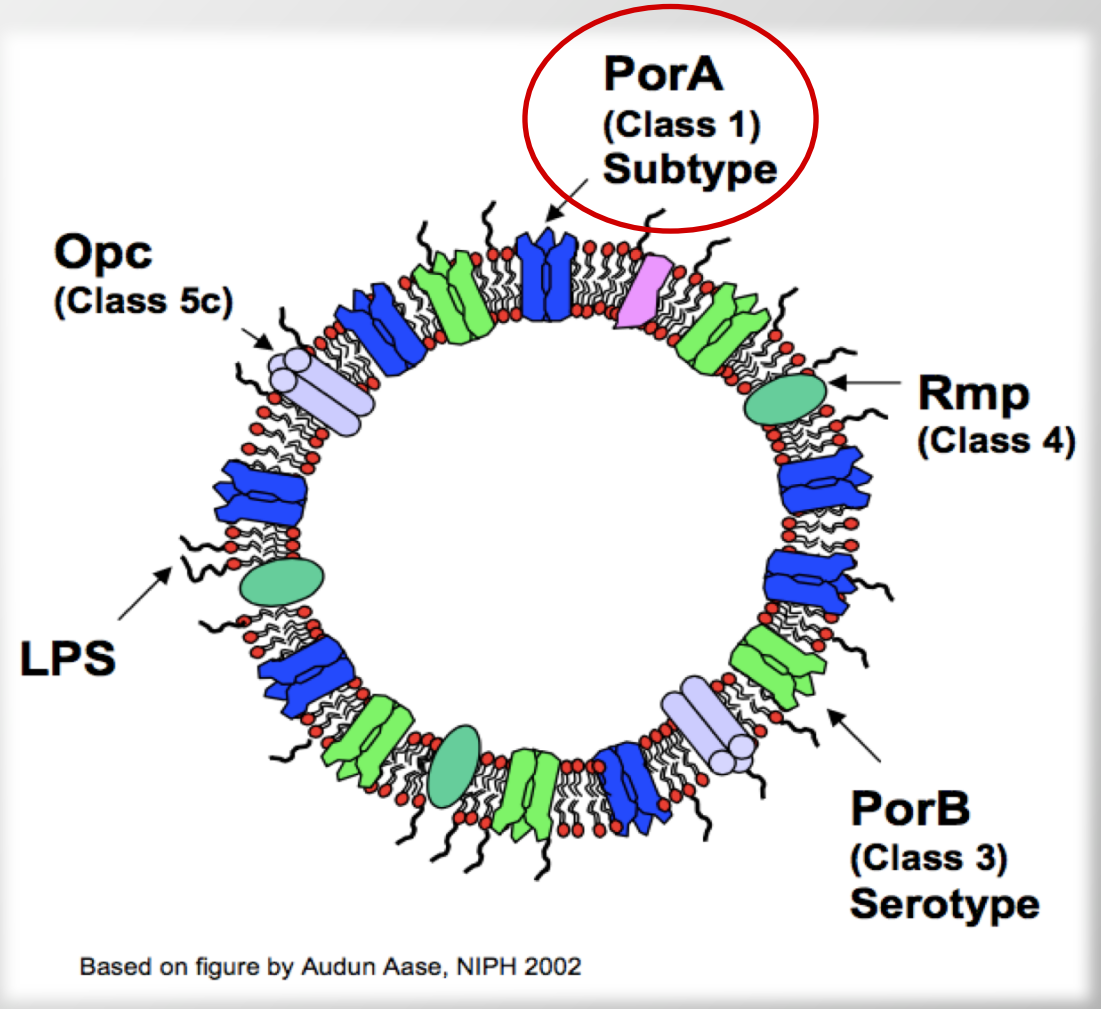
2 - Outer Membrane Protein Vesicles-based vaccine

Neisseria cells normally release vesicles, composed by OMPs, lipids and periplasmic components.

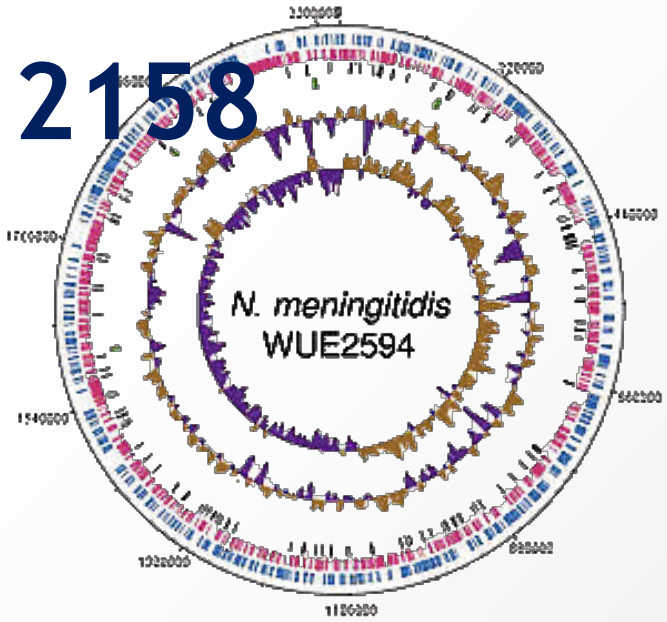
OMVs contain more than 70 proteins: the most abundant and immunogenic are porines (PorA).

Porines may be good vaccine candidates but have a high variability.

These are ideal vaccines just in case of clonal epidemies, only against the homologous strain.



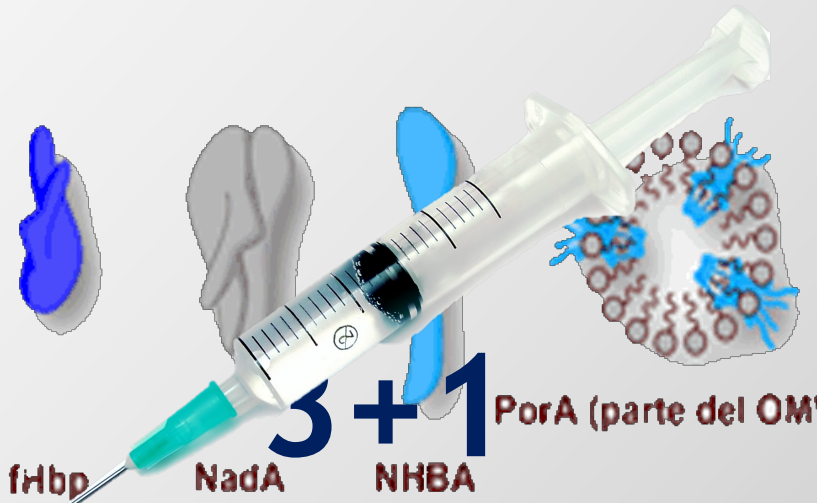
"TAILOR-MADE" MenB vaccines



2158

570

350



3 + 1

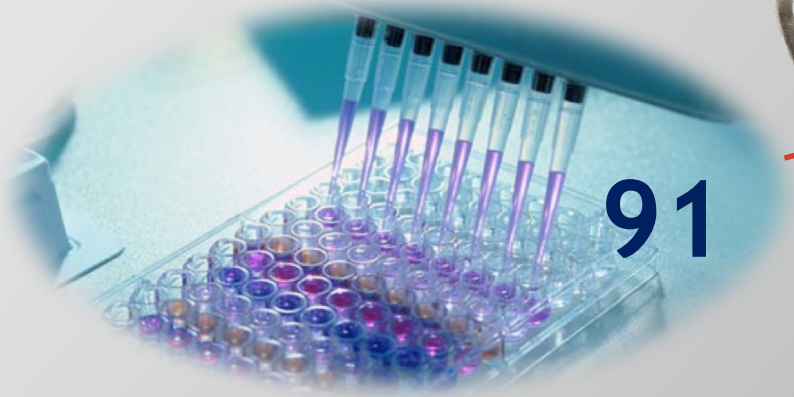
fHbp

NadA

NHBA

PorA (parte del OMV)

28



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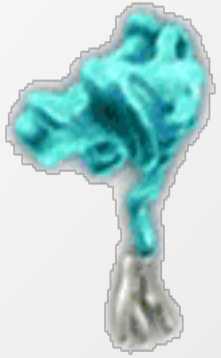
4CMenB composition

NadA

Neisseria adhesin A

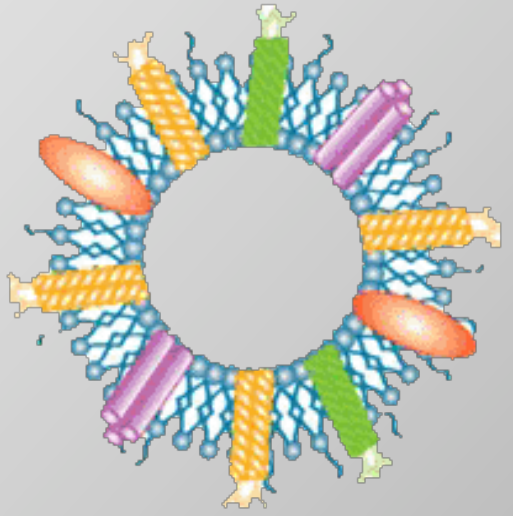


fHbp

Factor H binding protein

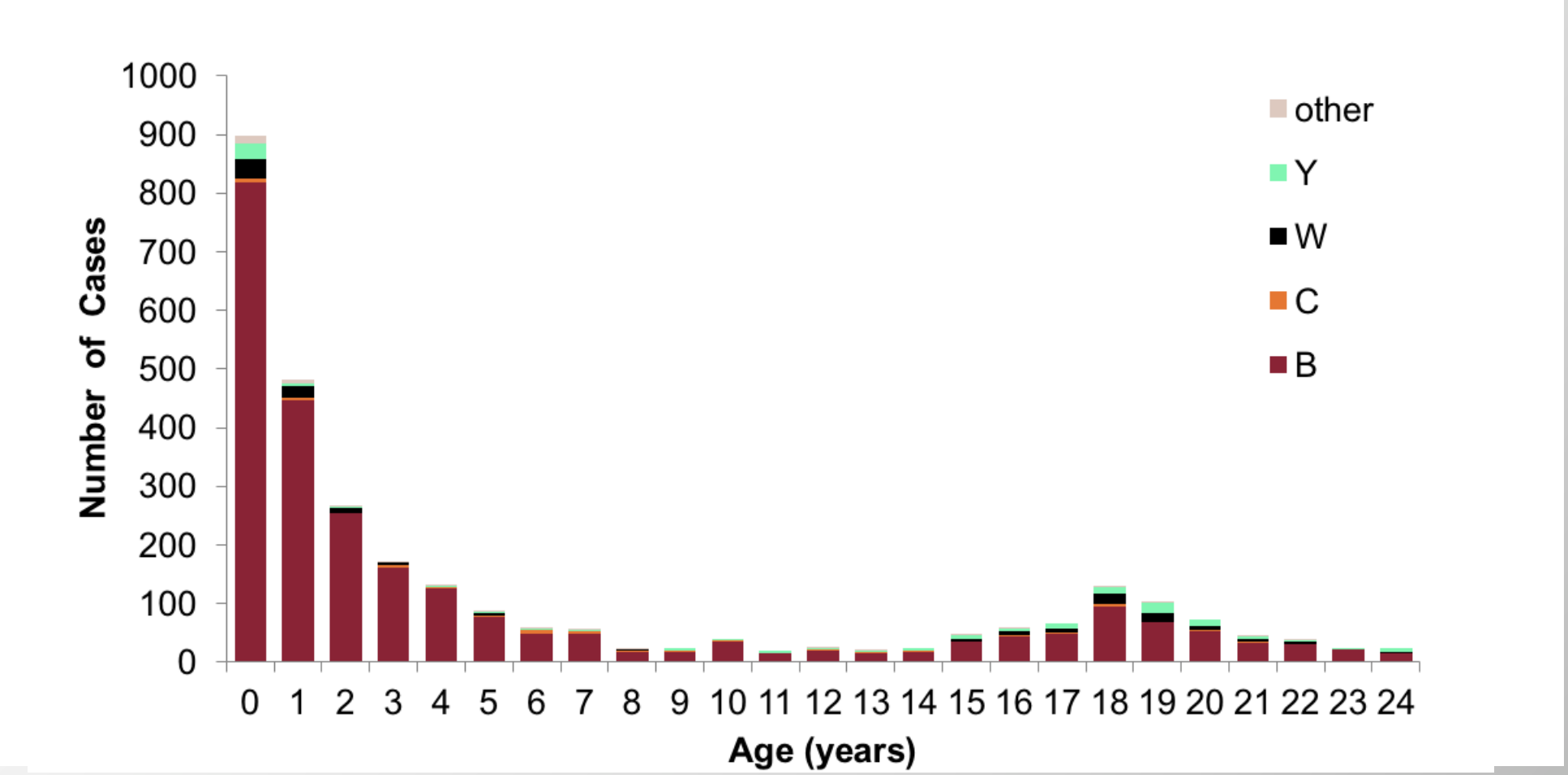
NHBA

Neisserial heparin binding antigen



Porine A

Epidemiological overview



Laboratory confirmed cases IMD
England and Wales

Epidemiological overview

4CMenB licensed since 2012

Estimated coverage (88% of MenB strains)

Infants and toddlers

WAITING FOR MoRe DATA

GRAZIE PER L'ATTENZIONE

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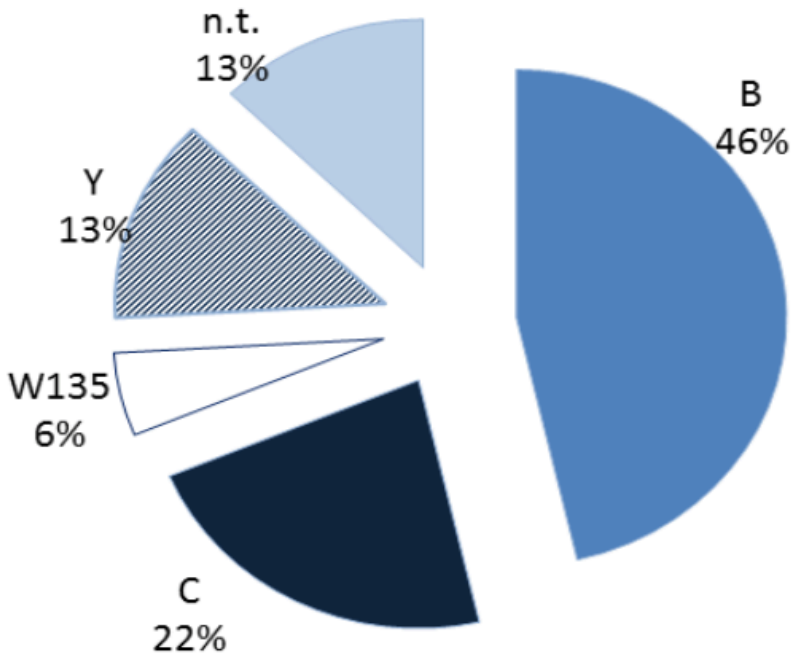
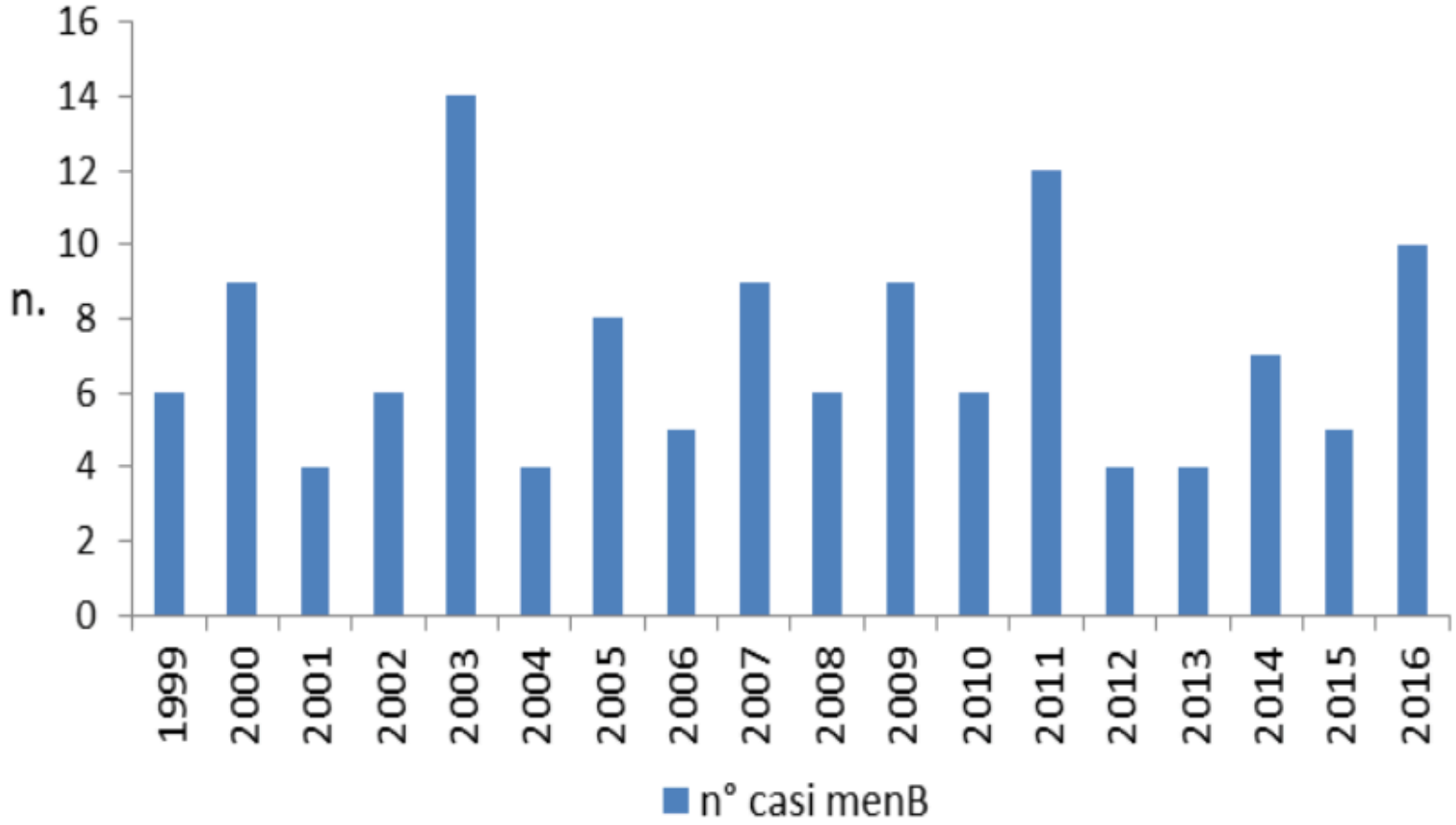
Distribuzione % dei casi di meningococco per sierogruppo. Emilia-Romagna, 2006-2016



Andamento dei casi di meningococco B (n° assoluto di casi). Emilia-Romagna 1999-2016



One dose (0.5 ml) contains:

1) Recombinant *Neisseria meningitidis* group B **NHBA** fusion protein (50 µg)

2) Recombinant *Neisseria meningitidis* group B **NadA** protein (50 µg)

3) Recombinant *Neisseria meningitidis* group B **fHbp** fusion protein (50 µg)

4) OMV from Neisseria meningitidis group B strain NZ98/254
measured as amount of total protein containing the **PorA** P1.4 (25 µg)

Other ingredients in the vaccine include: aluminium hydroxide, histidine, sodium chloride, sucrose, water for injections.

The vaccine is given by deep intramuscular injection, preferably in the anterolateral aspect of the thigh in infants or in the deltoid muscle region of the upper arm in older subjects.

Adapted from “Bexsero Meningococcal Group B vaccine for injection in pre-filled syringe”, GlaxoSmithKline UK

MATS (Meningococcal Antigen Typing System)

1) Are any of the selected proteins in the test strain expressed to a sufficient degree?

2) Are they similar enough to the antigens in the vaccine such that the antibodies generated will kill the bacteria?

MATS ELISA determines the minimum amount (termed relative potency) of recognisable antigen needed to result in bacterial killing for each of fHbp, NadA and NHBA (PorA characterised by sero/genotyping).

For a strain to be “covered”, at least one antigen MATS must be greater than the positive bactericidal threshold (PBT) or possess homologous PorA (P1.4).

Adapted from “Issues in evaluating the impact of a new meningococcal B vaccine”, Borrow R.