Ricerca e sviluppo e utilizzo di vaccini contro il meningococco

Rino Rappuoli

XXI congresso Nazionale SIPPS

Siena 1 giugno 2009

NOVARTIS VACCINES

Meningococcal disease

caused by *Neisseria meningitidis* capsular serotypes A, B, C, Y , W_{135}

EXCLUSIVE

By EMMA MORTON
and LUCY LAING

Published: 11 Apr 2009

ADD YOUR COMMENTS

THE Sun
Monday, April 20, 2009

LITTLE battler Ellie Challis has a real spring in her step — after becoming the youngest person ever fitted with bouncy flex-foot artificial legs.

The five year old — who lost her limbs in 2005 when she almost died from meningitis — had the £10,000 carbon frames specially made.

They are the same type as the legs used by disabled athlete Oscar Pistorius and wounded Marines hero Ben McBean, with a C-shaped foot for added bounce.

Battler ... Ellie Challis with mum, dad, and twin Sophie

Step it up ... Ellie Challis tests out her new legs

Heroes ... Oscar Pistorius and Ben McBean

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Meningococcal disease

caused by

Neisseria meningitidis capsular serotypes

A, B, C, Y , W_{135}

WEDNESDAY, OCTOBER 11, 2006

SAN FRANCISCO

School takes preca
11-year-old dies of

Spread is rare, but her classmates told to take antibiotics

By Jill Tucker and Sabin Russell
CHRONICLE STAFF WRITERS

isco Chronicle

OCTOBER 11, 2006

The well-liked child, Evelyn Cortez-Covarrubias, attended school on Friday and complained of a stomachache, Packer said. Her condition quickly worsened and she died three days later

Death

An 11 year old died

Severe disability

Teen loses parts of legs and hands to beat deadly

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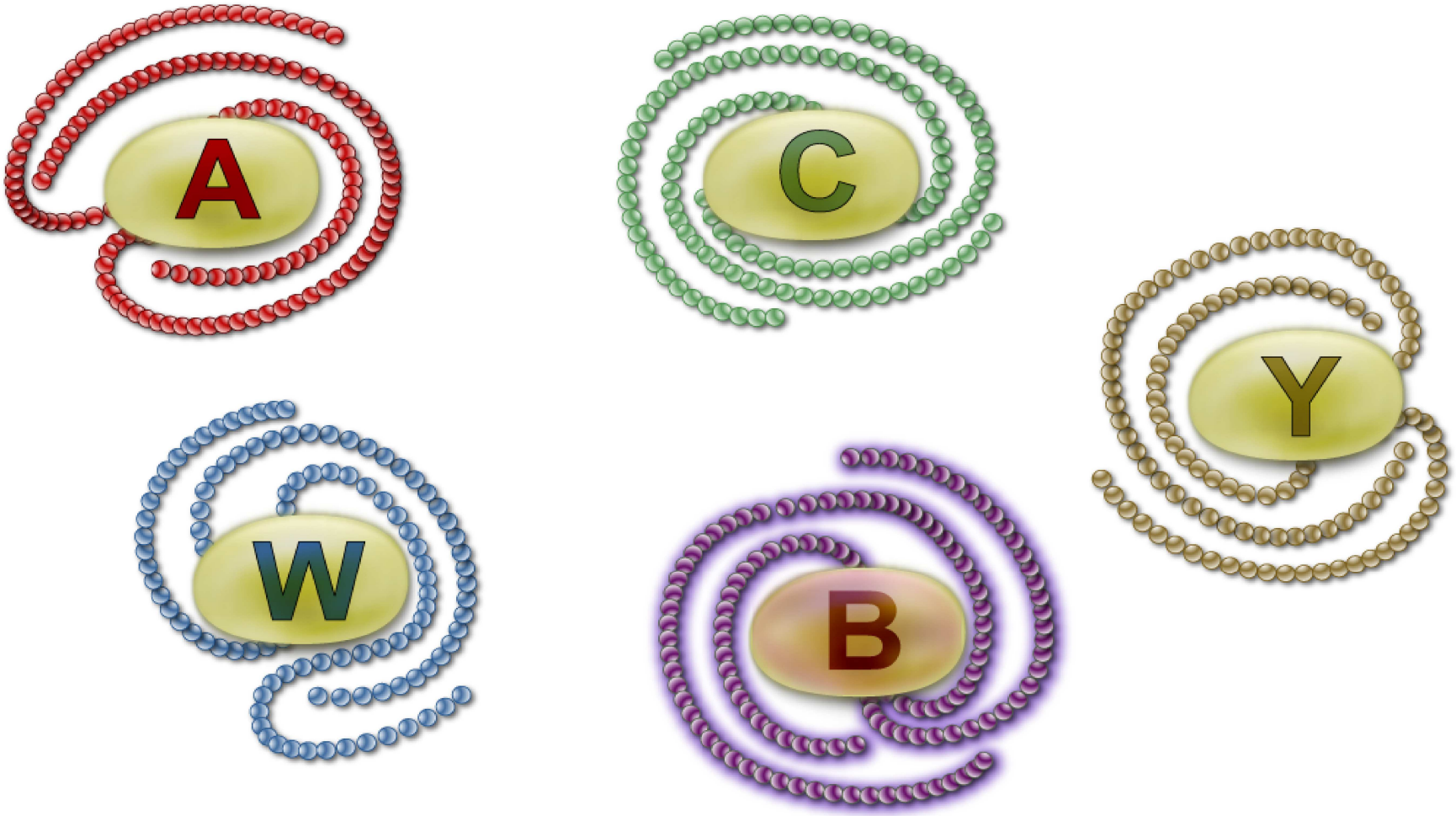
N meningitidis has Many Serotypes – Each with a Distinctive Coat Polysaccharide



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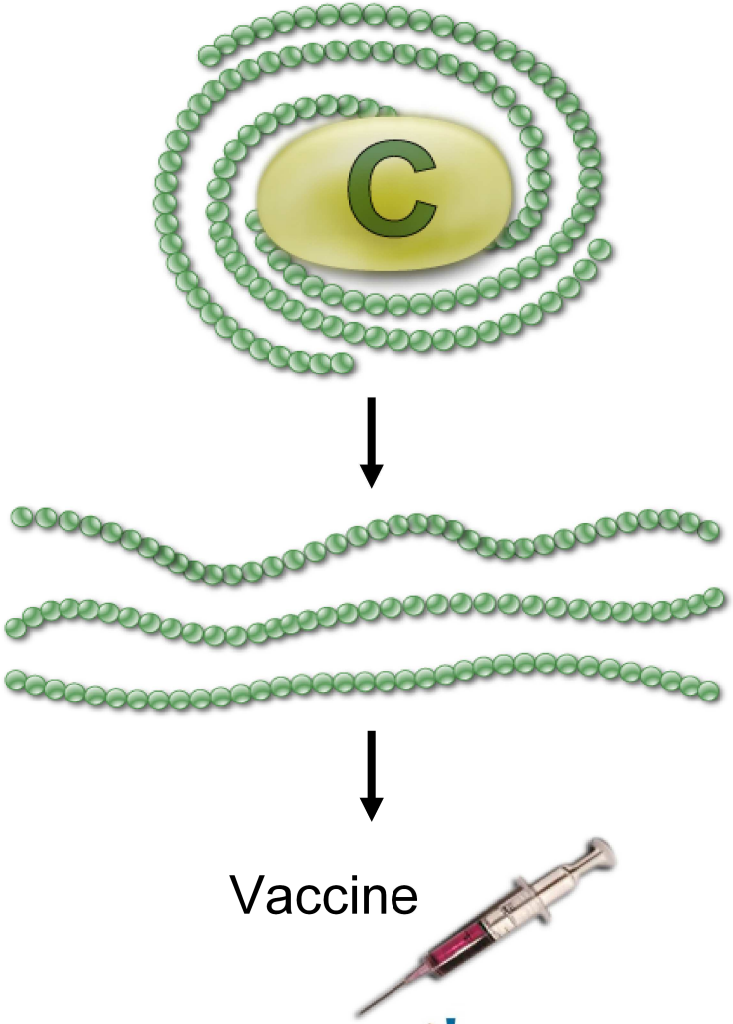
Polysaccharides are not Good Vaccine Antigens

Polysaccharides trigger a limited immune response

- B cell response only
- Lacks potency, durability and memory (boost)

Infants do not respond to polysaccharide vaccines



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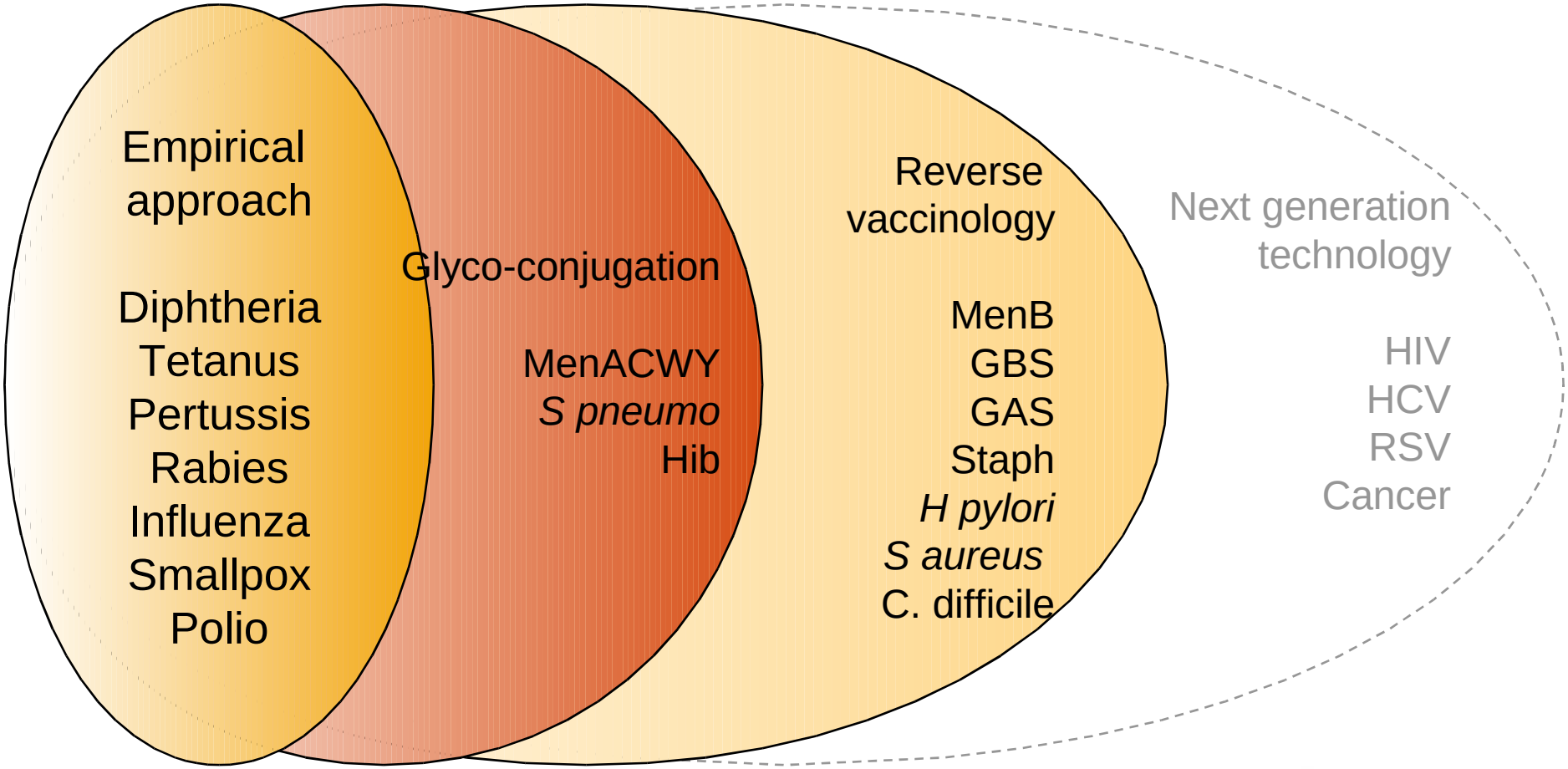
New technologies during the last 30 years expand the pool of vaccine targets



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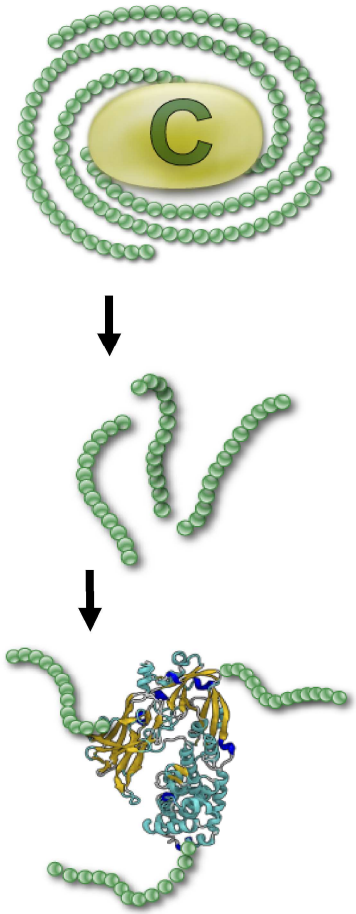
Glycoconjugation Improves the Immunogenicity of Polysaccharides



C antigen

A glycoconjugate against serotype C was developed early 1990's

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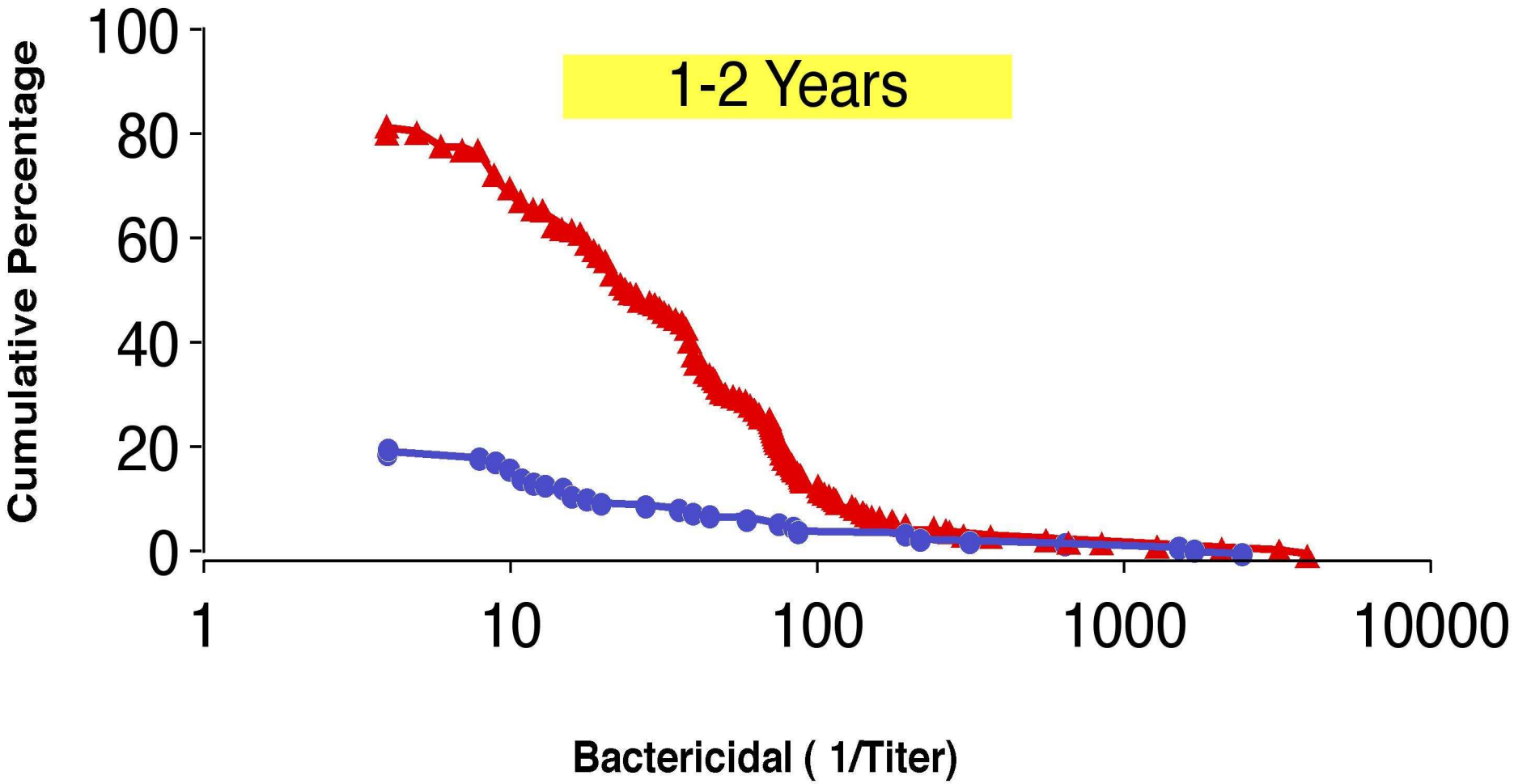
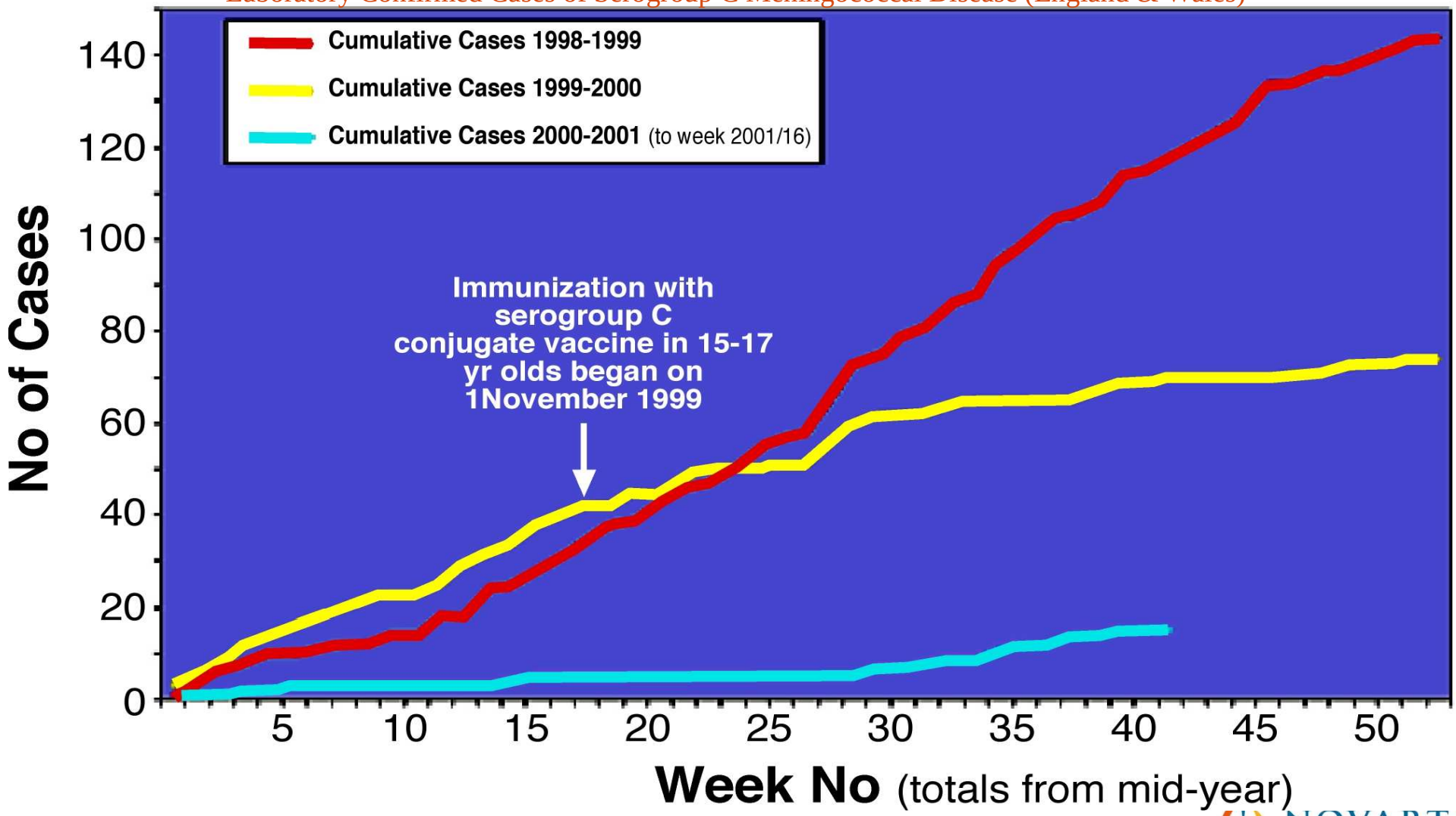
MenC Conjugate Vaccine (red) Induced high level of Bactericidal Antibodies in Infants. Plain Polysaccharide (blue) was a poor Immunogen



Conjugate vaccines for Meningococcus C Eliminated the Disease in the UK

Laboratory Confirmed Cases of Serogroup C Meningococcal Disease (England & Wales)



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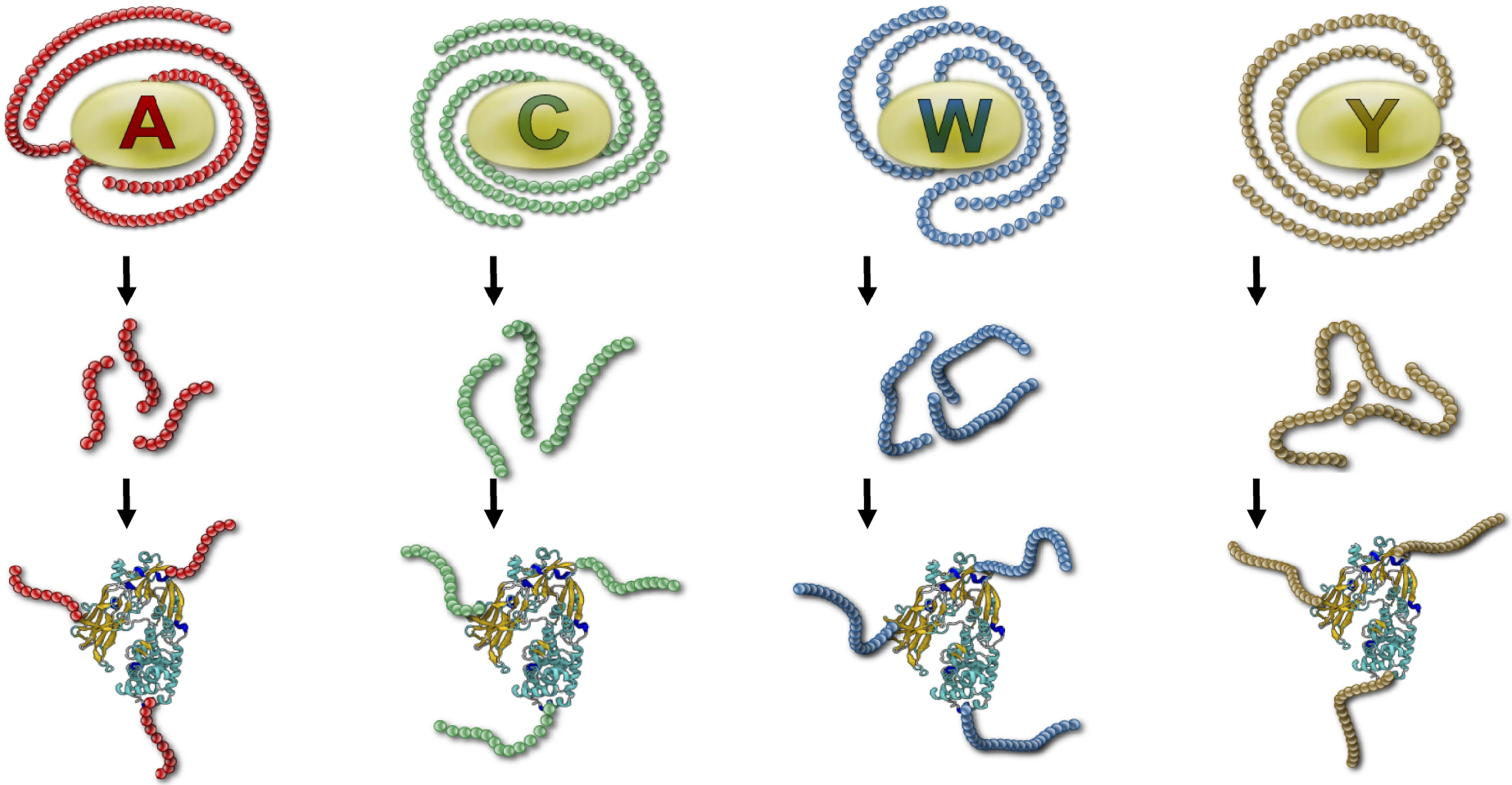
Menveo® was Developed to Protect All Ages Against Meningococcus A,C,Y, W



A antigen C antigen W antigen Y antigen

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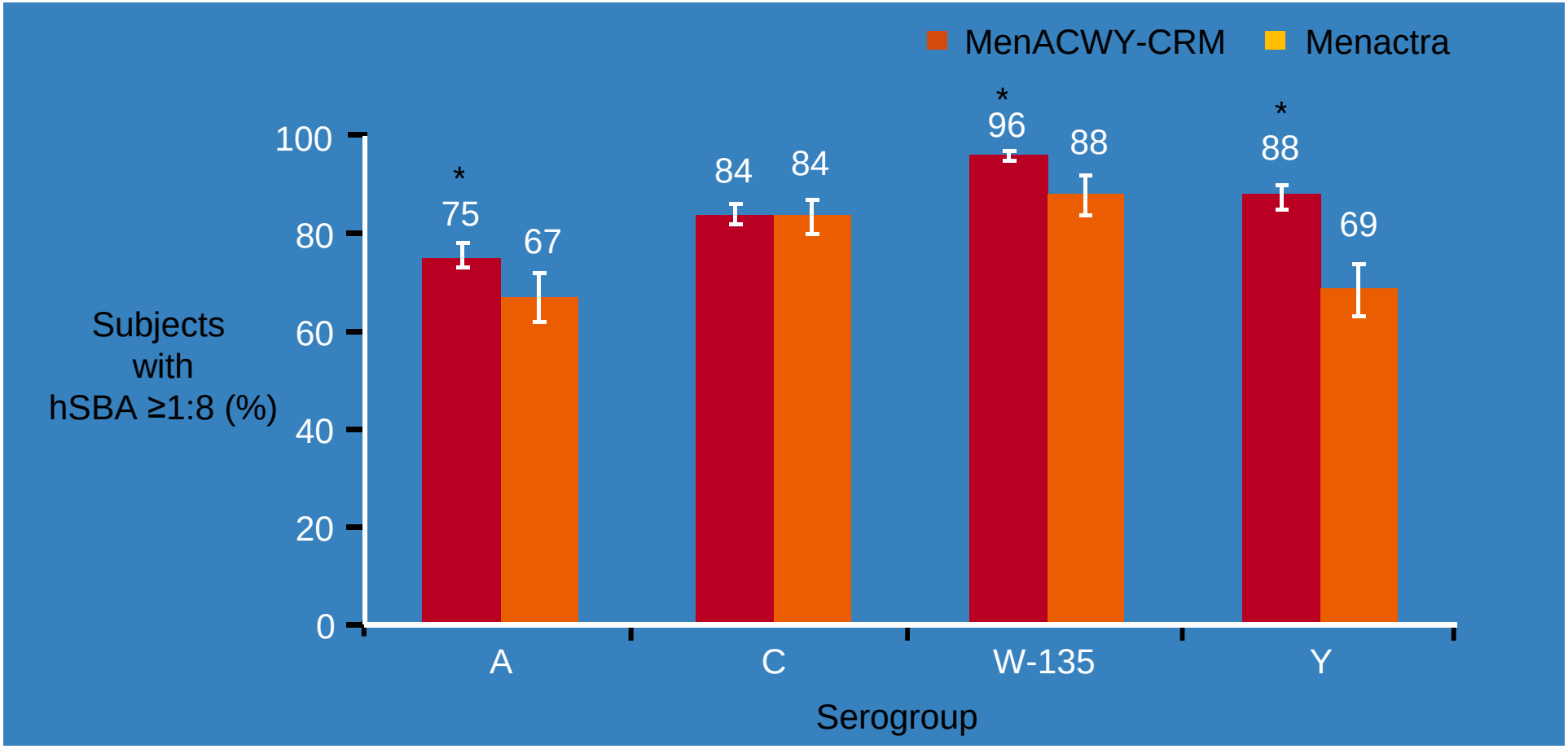
Phase III immunogenicity in adolescents

hSBA titers ≥1:8 1 month post-vaccination



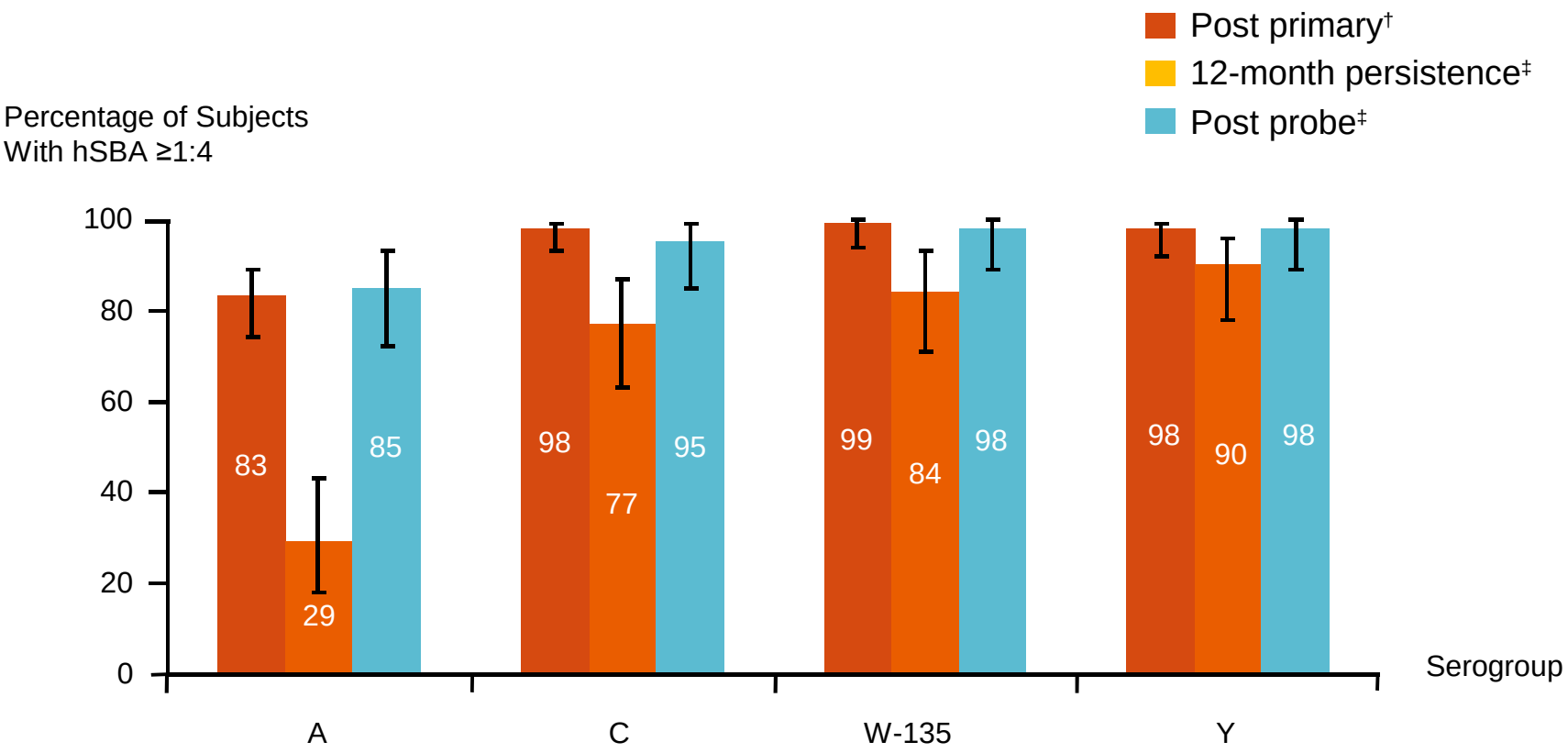
*Met the criteria for statistical superiority LL 95% CI of difference (MenACWY-CRM minus Menactra) >0%
Per-protocol population. MenACWY-CRM n=1024-1483 per serogroup; Menactra n=288-501 per serogroup
Presented at: Pediatric Academic Societies and Asian Society for Pediatric Research Joint Meeting; May 2-6, 2008; Honolulu, Hawaii
Data on file, Novartis Vaccines

Study V59P13 US

Menveo® is Highly Immunogenic in Infants

Phase II Immunogenicity in Infants

MenACWY-CRM* given at 2, 4, and 6 months, and polysaccharide probe at 12 months



*With aluminum phosphate adjuvant; †n=98; ‡n=49.

Snape MD et al. *JAMA.* 2008;299:173-84; Perrett KP et al. *Pediatr Infect Dis J.* 2009;28:186-193.

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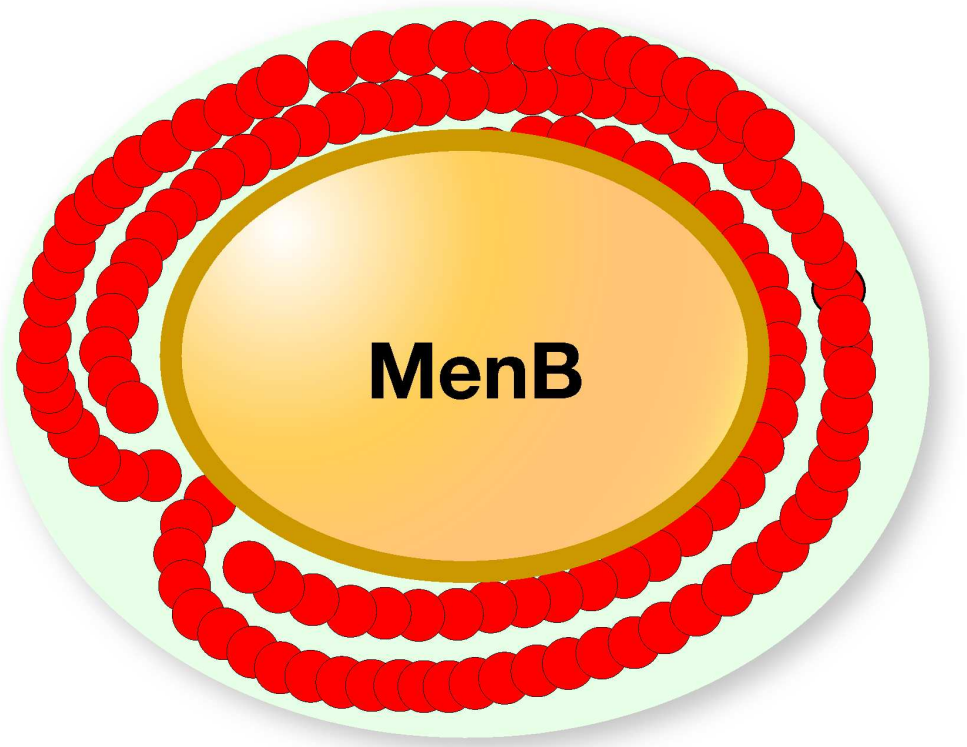
Meningococcus B capsule
a self antigen cannot be used for vaccination



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Vaccinologists Have Tried for Many Years to Develop a Vaccine for MenB Without Success

Polysaccharide vaccines	OMV[1] vaccines	Purified proteins
1980s	1990s	2000s
Failed: Self antigen - unable to trigger a response	Failed: Insufficient strain coverage	Failed: Poorly immunogenic and insufficient strain coverage

[1] *Outer membrane vesicle*

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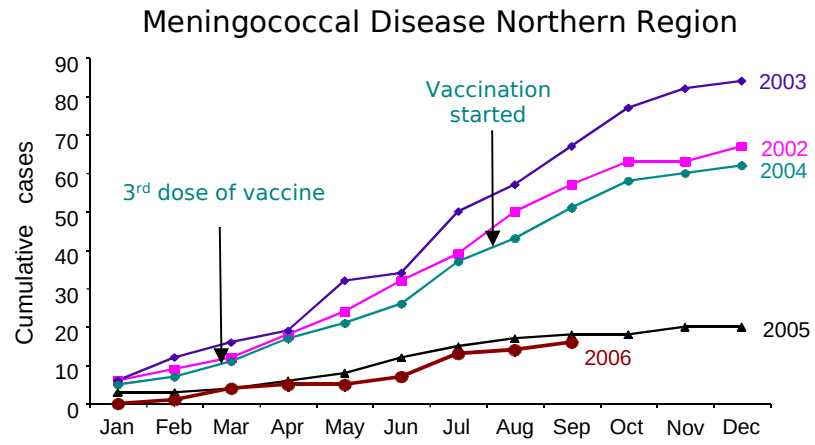
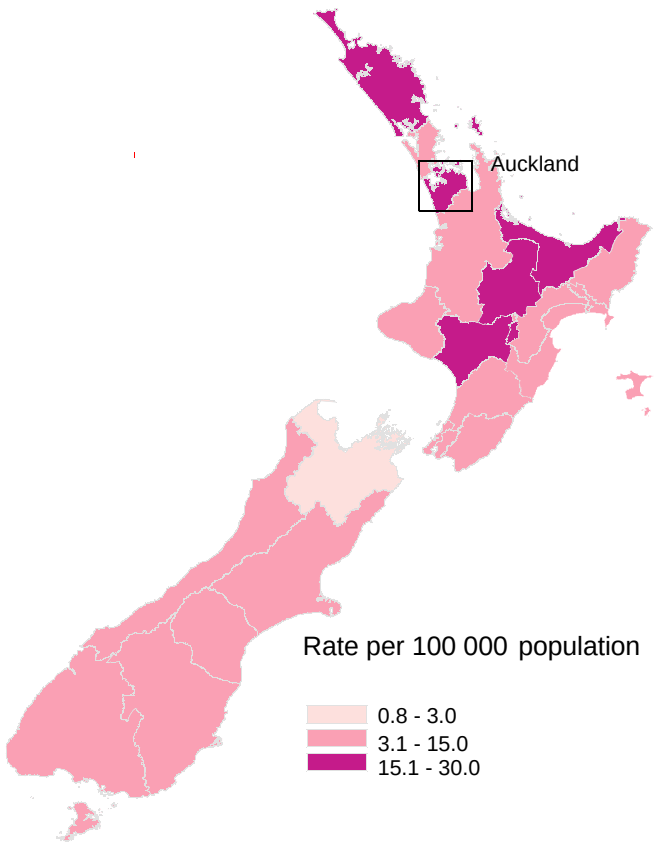
Meningococcus B, OMV was successful to Eliminate the Epidemic in New Zealand





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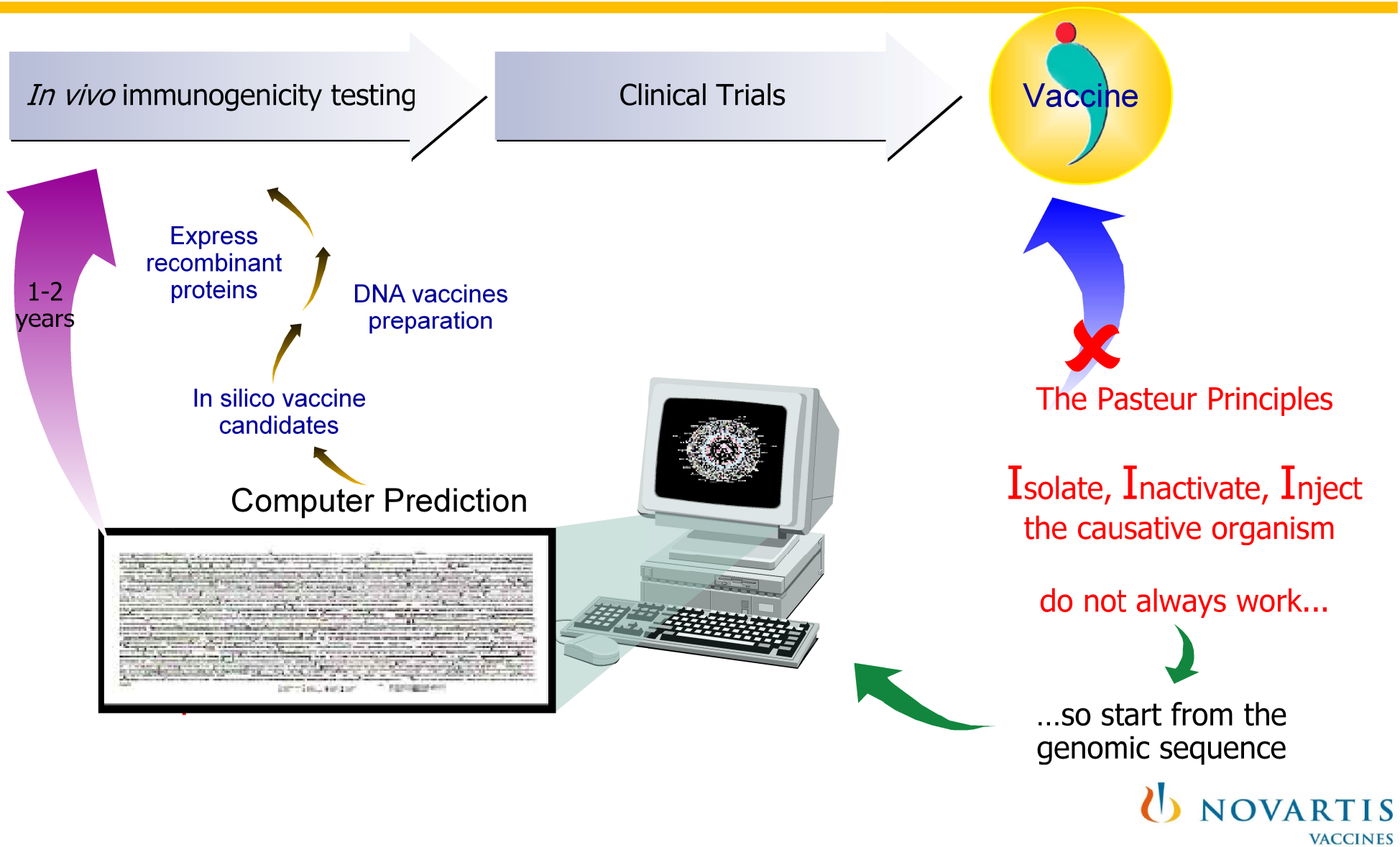
Reverse Vaccinology



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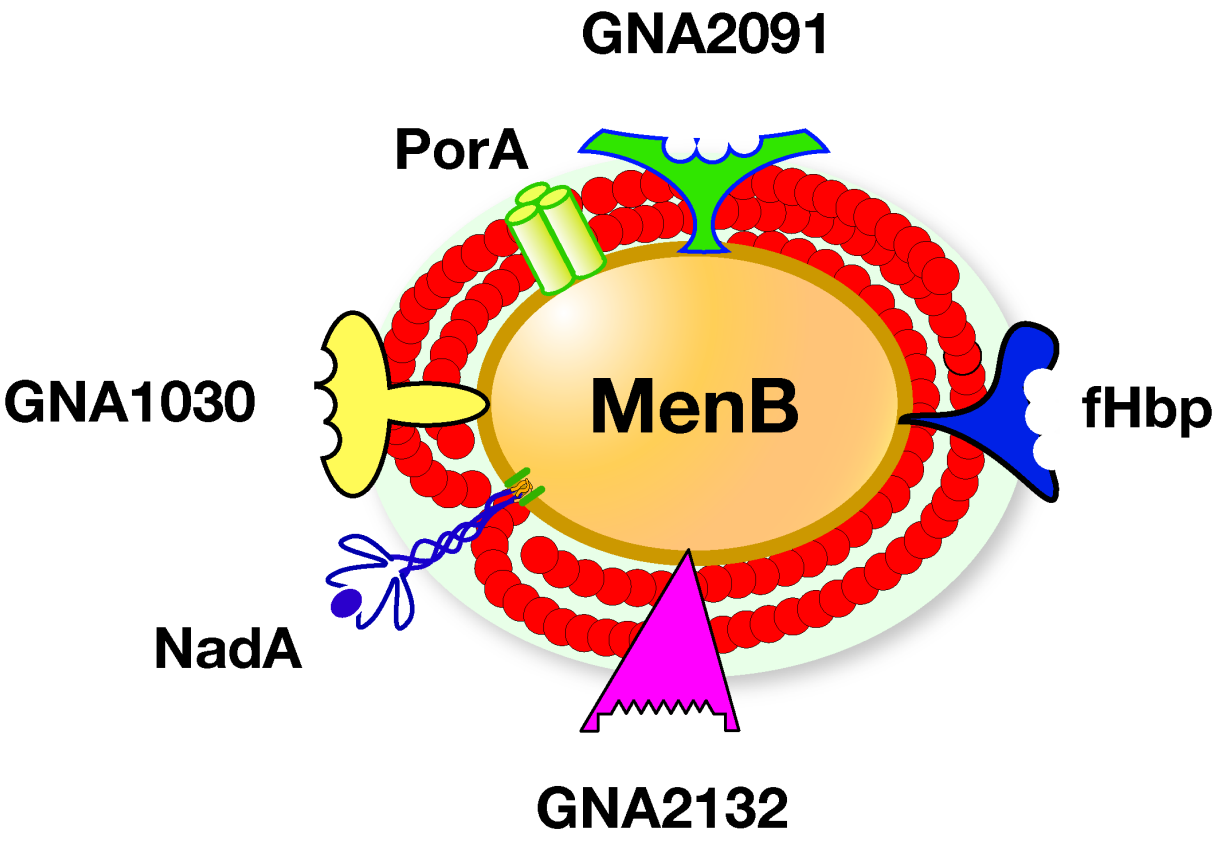
New surface proteins were discovered
5 were used to make a vaccine



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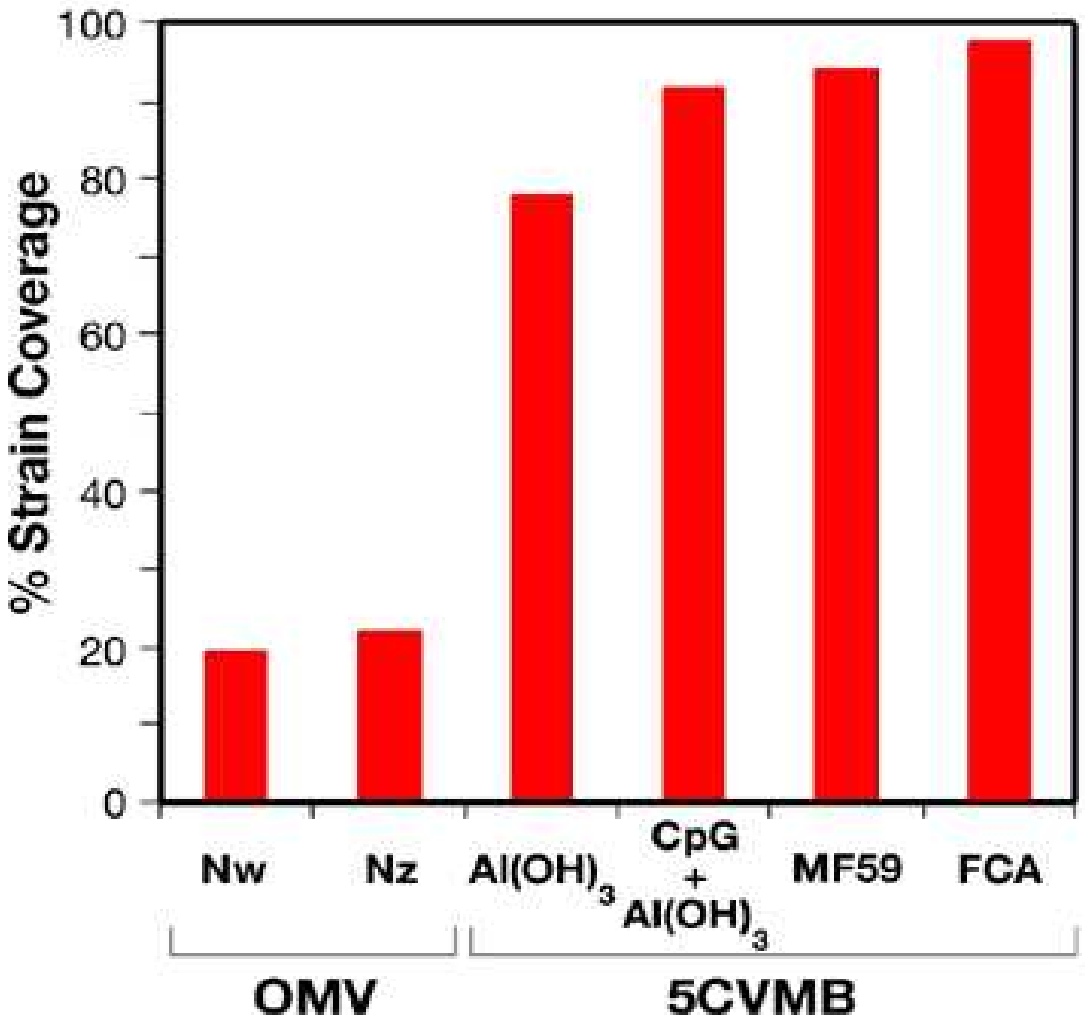
BCA Activity Against a Panel of 85 Strains Representative of the MenB Global Diversity



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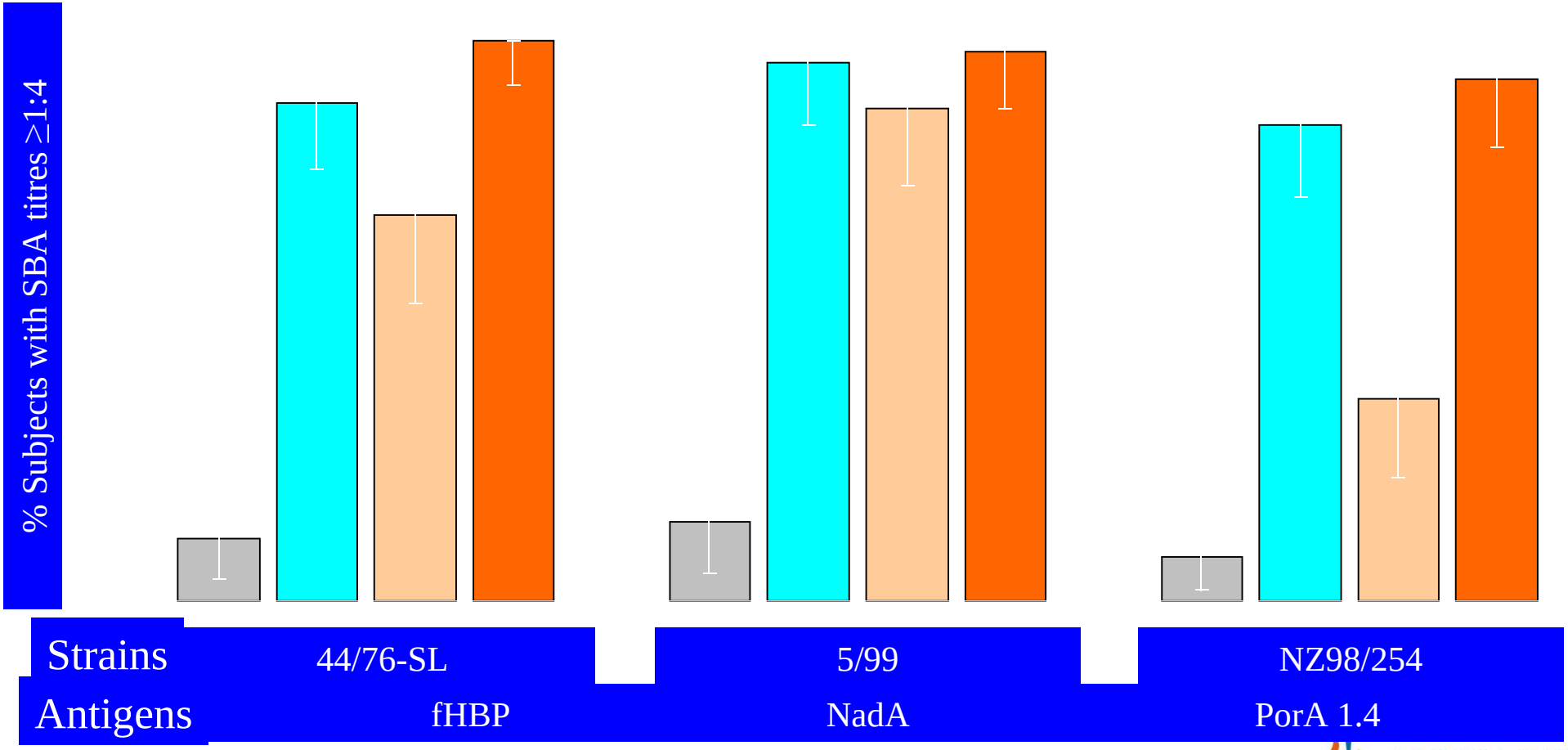
Men B Vaccine Works in Infants

Proportion of Subjects with hSBA Titres ≥1:4 Before & After MenB Vaccine



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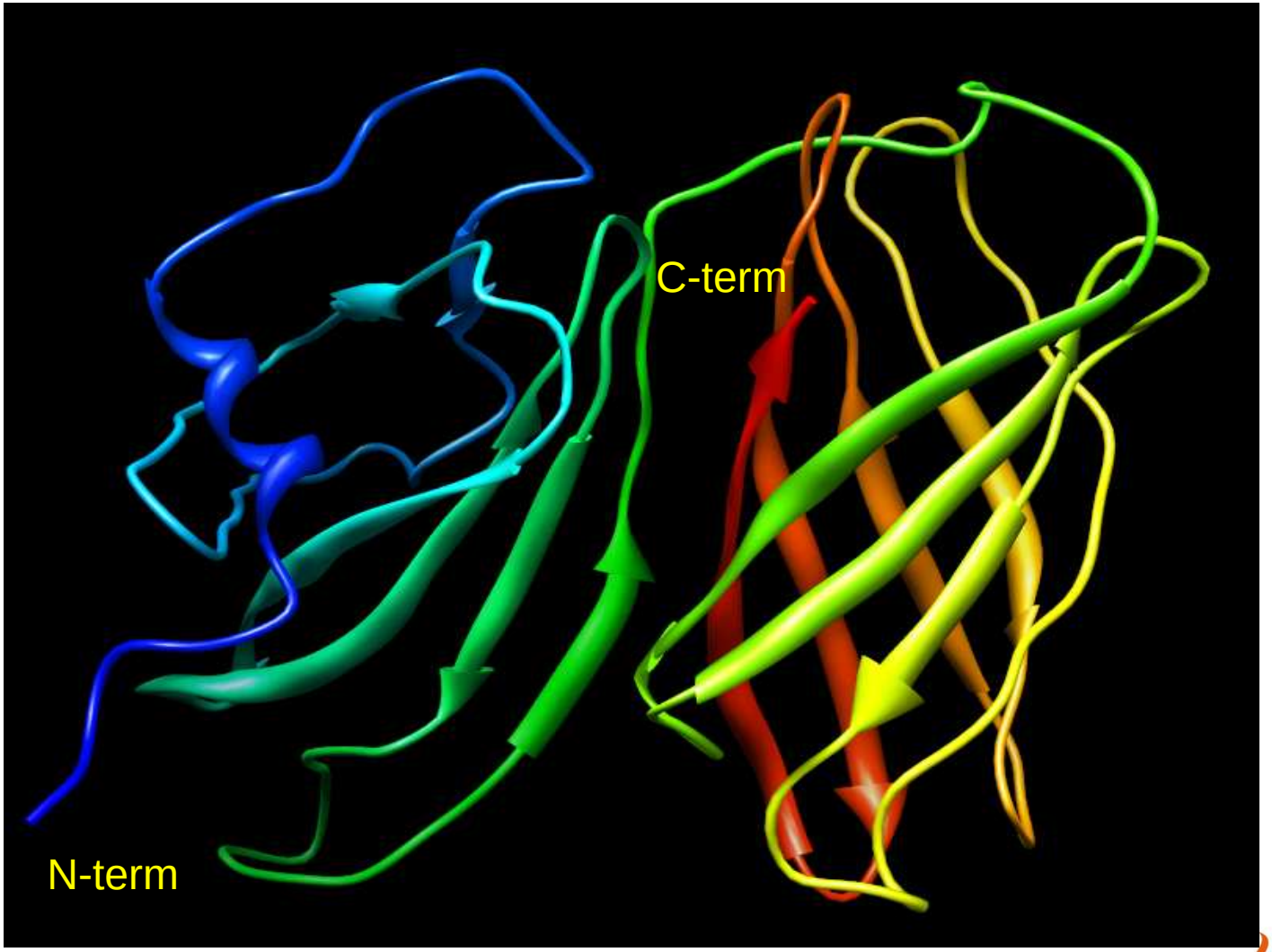
GNA 1870 binds Factor H

Factor H binding protein



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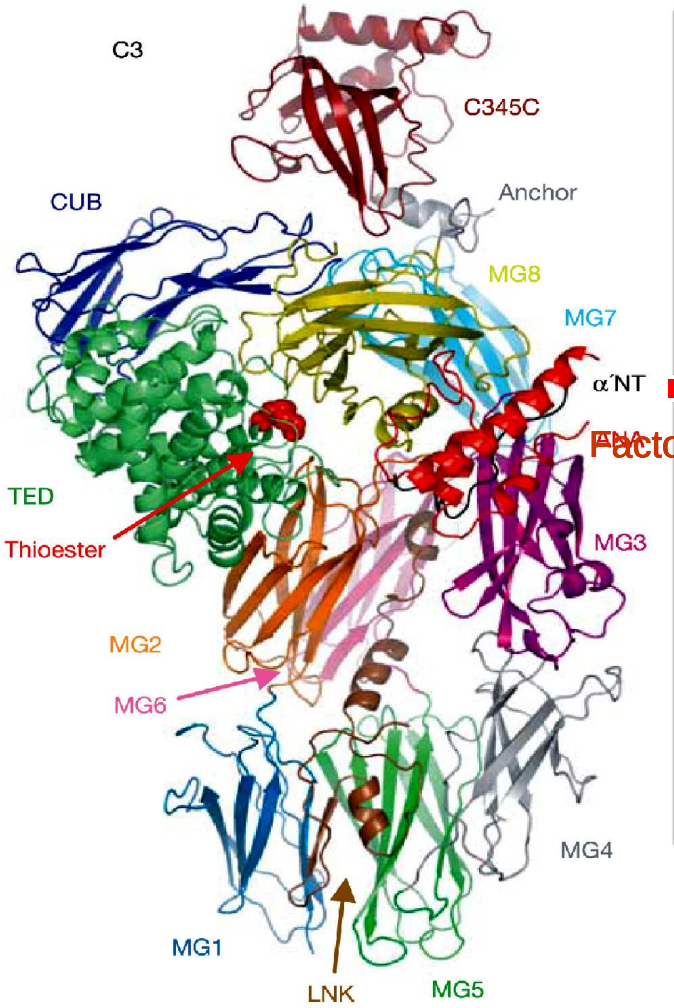
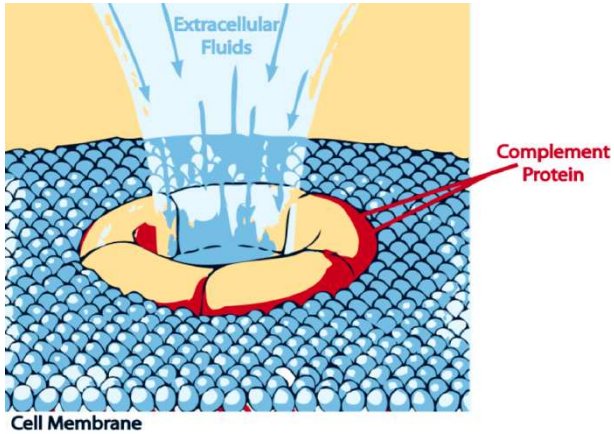
C3, the “fuel” of the complement cascade

(> 1g/liter in human plasma)



Bert J. C. Janssen[1], Eric G. Huizinga[1], Hans C. A. Raaijmakers[1], Anja Roos[2], Mohamed R. Daha[2], Kristina Nilsson-Ekdahl[3,4], Bo Nilsson[3] & Piet Gros[1]
NATURE|Vol 437|22 September 2005



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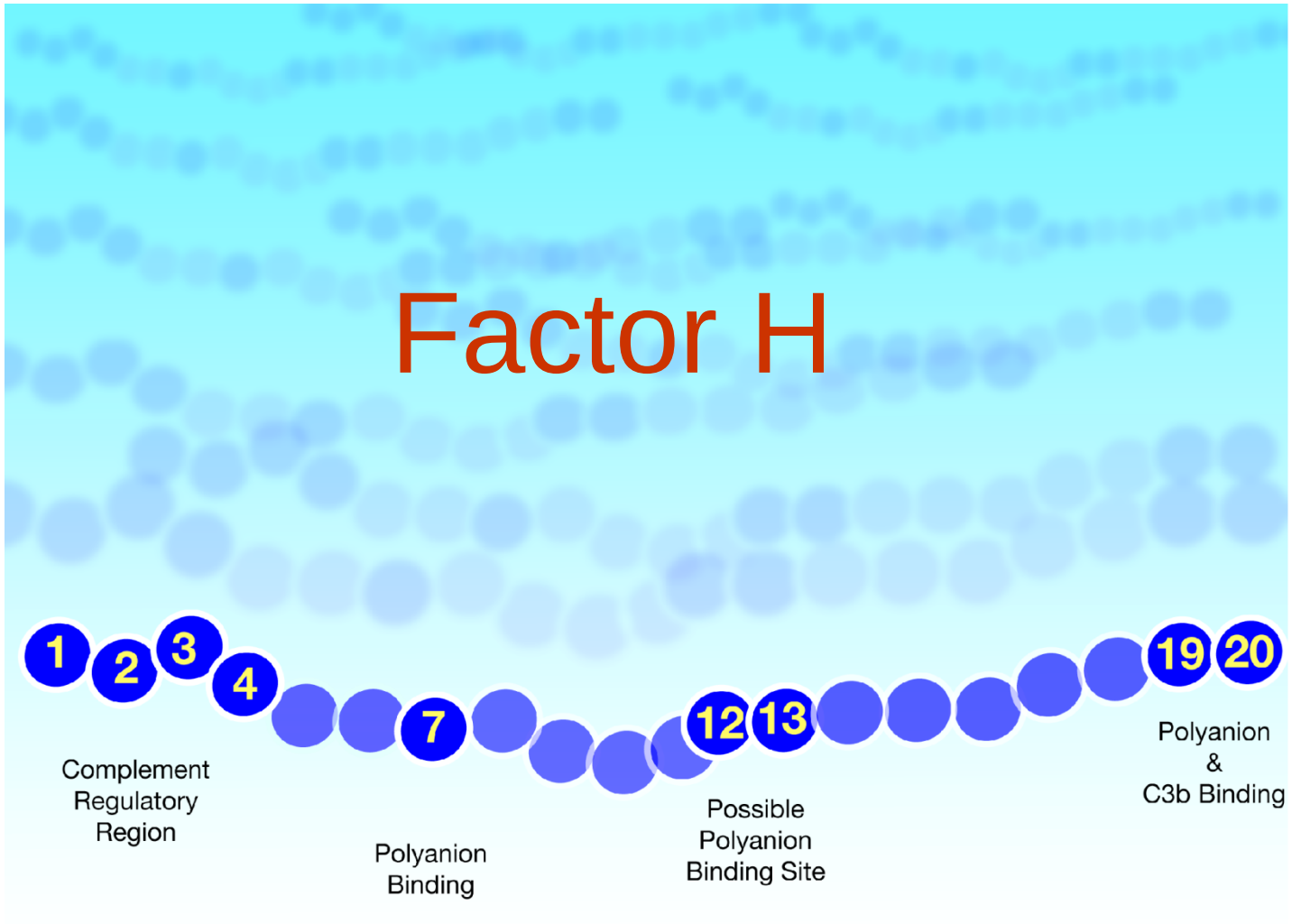
Factor H (>0.5 g/liter in the human plasma),coats all self tissues and cells and prevents C3 deposition



20 domains

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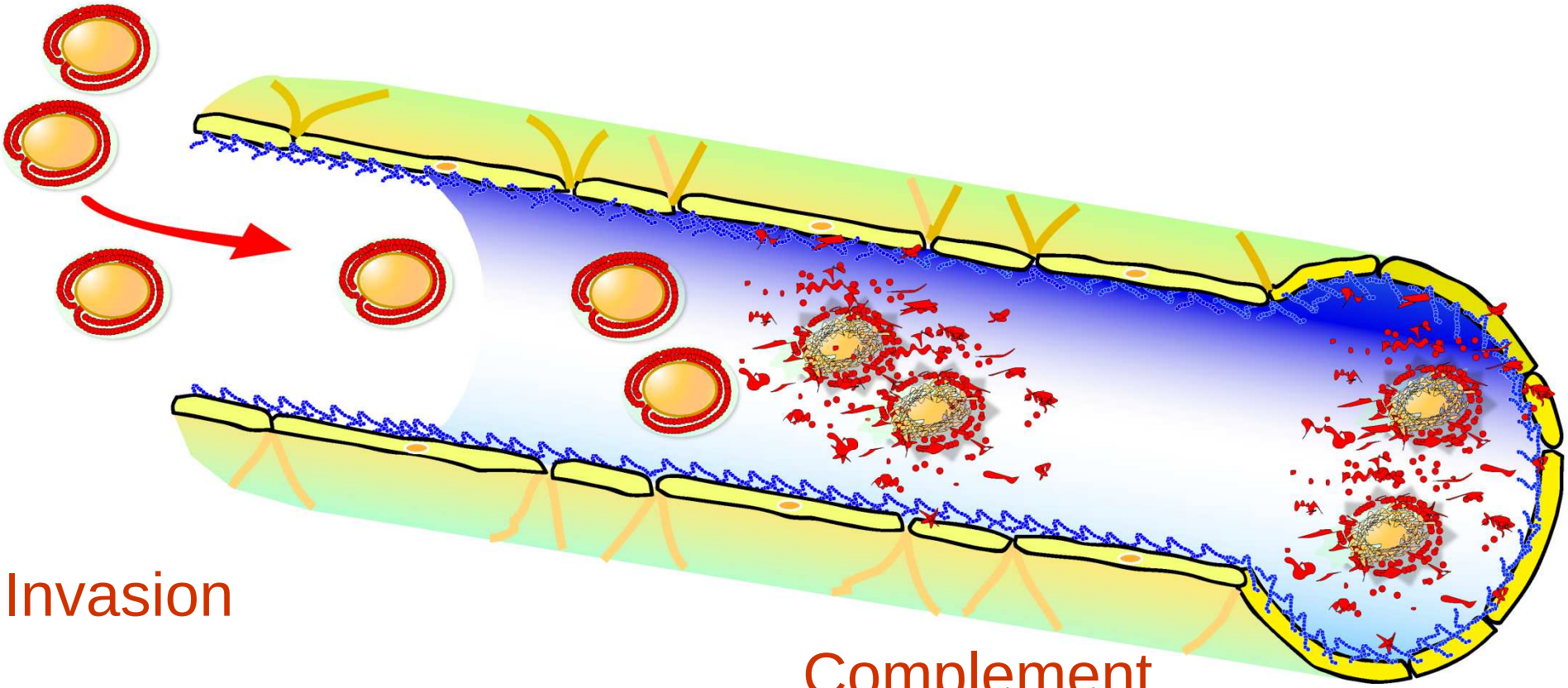
Bacteria are recognized as non self by the alternative pathway of complement, C3 binds and complement kills them



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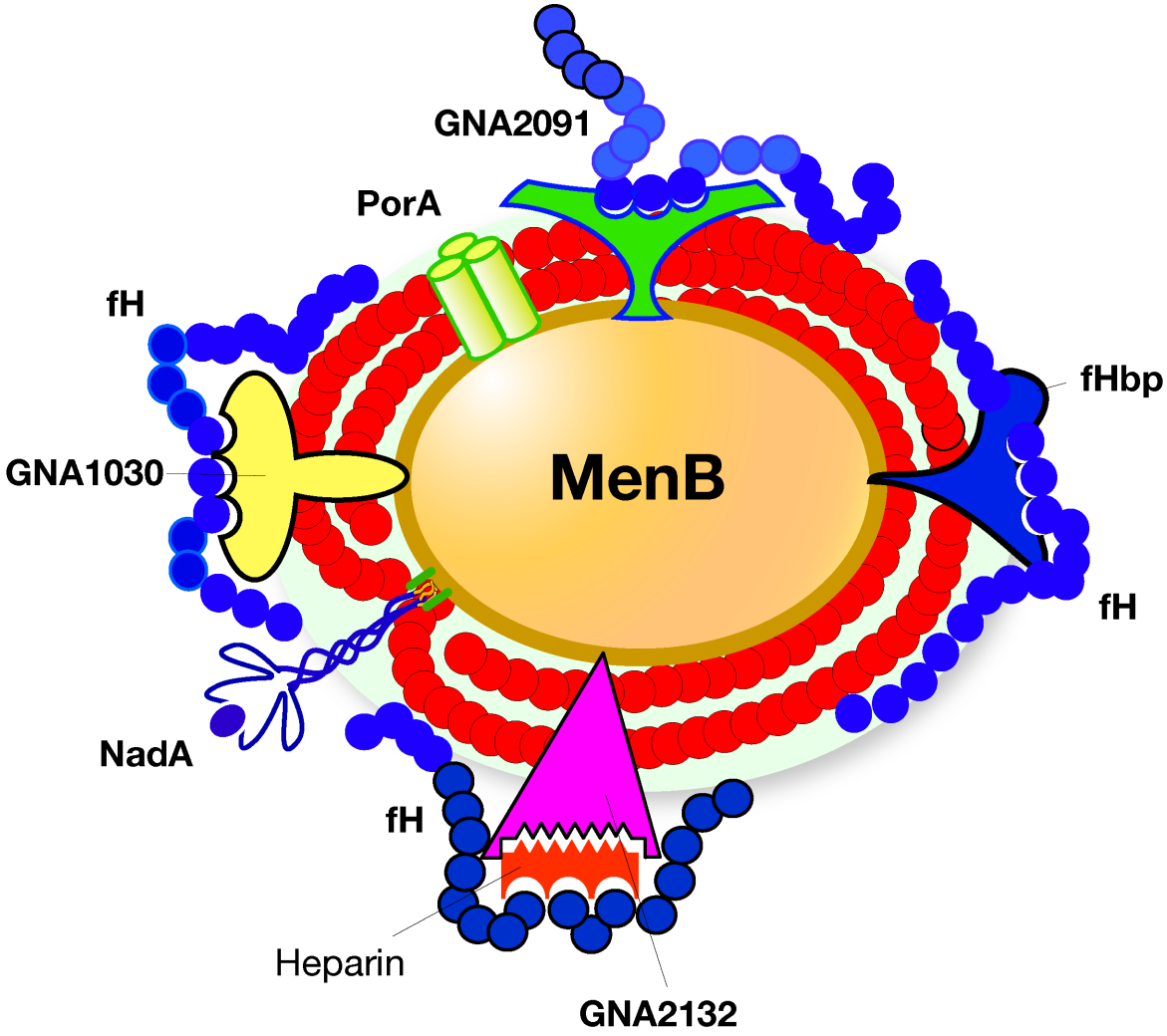
Binding factor H is a survival mechanism for meningococcus

Four of the five best antigens discovered and present in the vaccine bind Factor H



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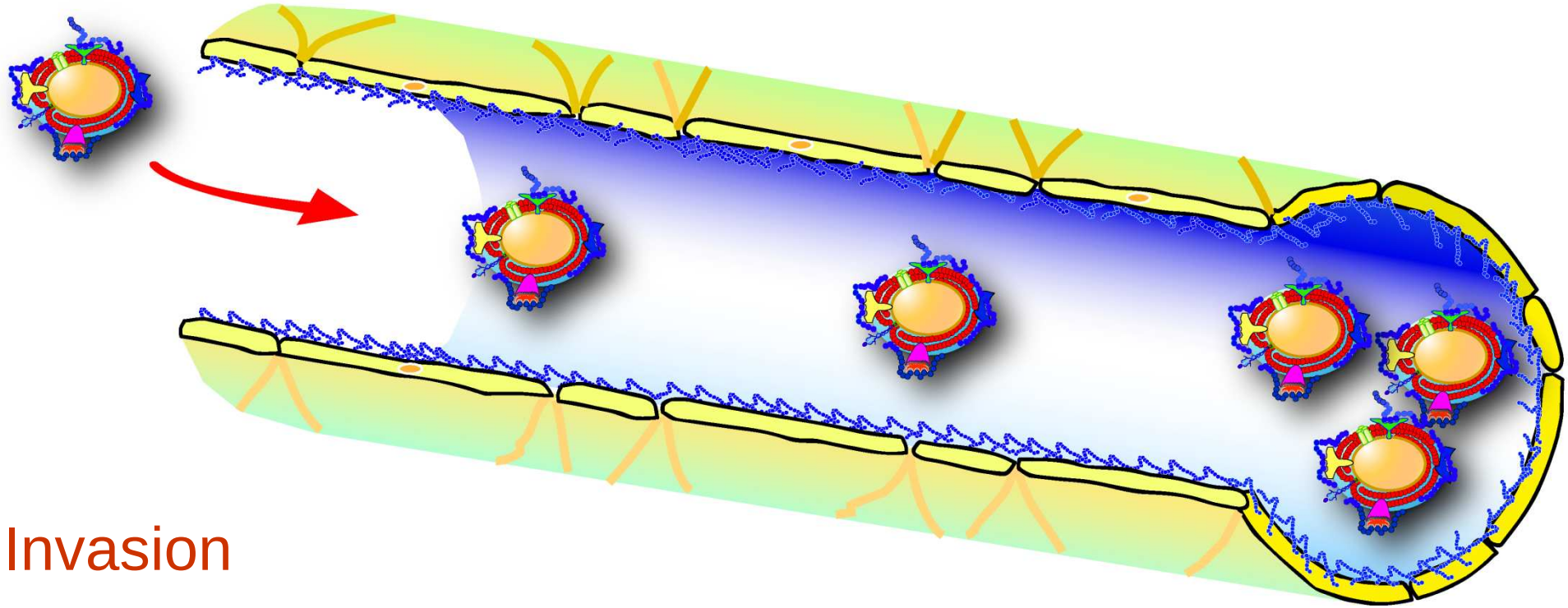
Neisseria meningitidis coated by Factor H is not recognized as non self by C3, survives and multiplies in human blood



Invasion

Survival and growth

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