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CORSO DI IGIENE

Scuola
di
Medicina

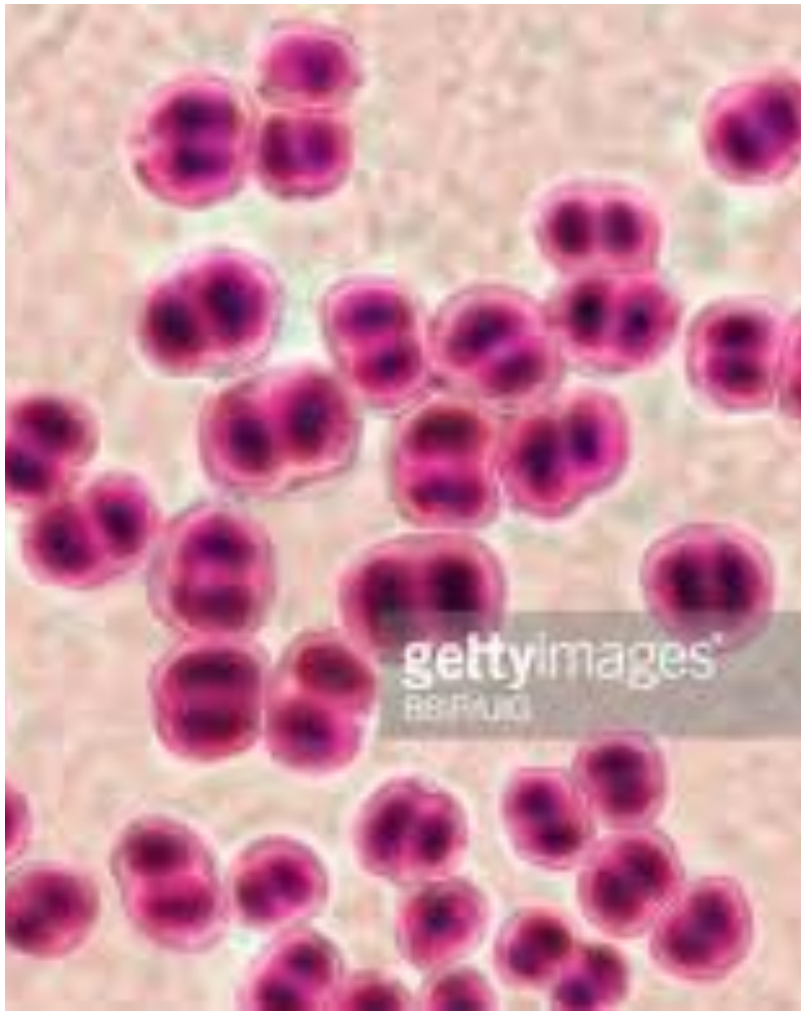
Meningococcal diseases

Neisseria meningitidis

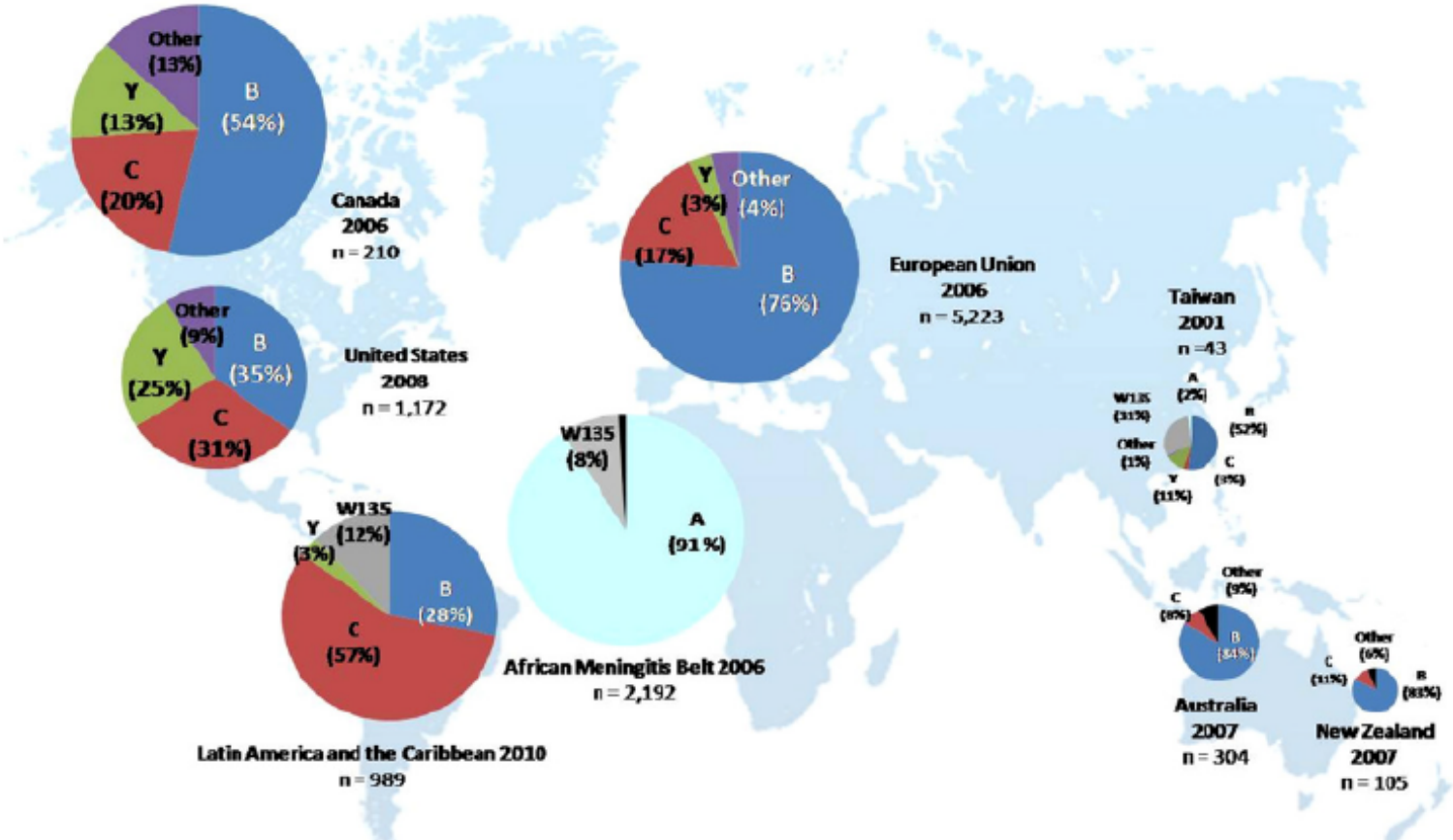
- Severe acute bacterial infection
- Cause of meningitis, sepsis, and focal disease (e.g. pneumonia and arthritis)
- Epidemic disease in sub-Saharan Africa
- Quadrivalent polysaccharide vaccine licensed in 1981

Neisseria meningitidis

- Aerobic gram-negative bacteria
- 13 distinct polysaccharide capsules have been described
- Almost all invasive disease caused by serogroups **A, B, C, Y, and W**
- Relative importance of serogroups depends on geographic location and other factors (e.g. age)

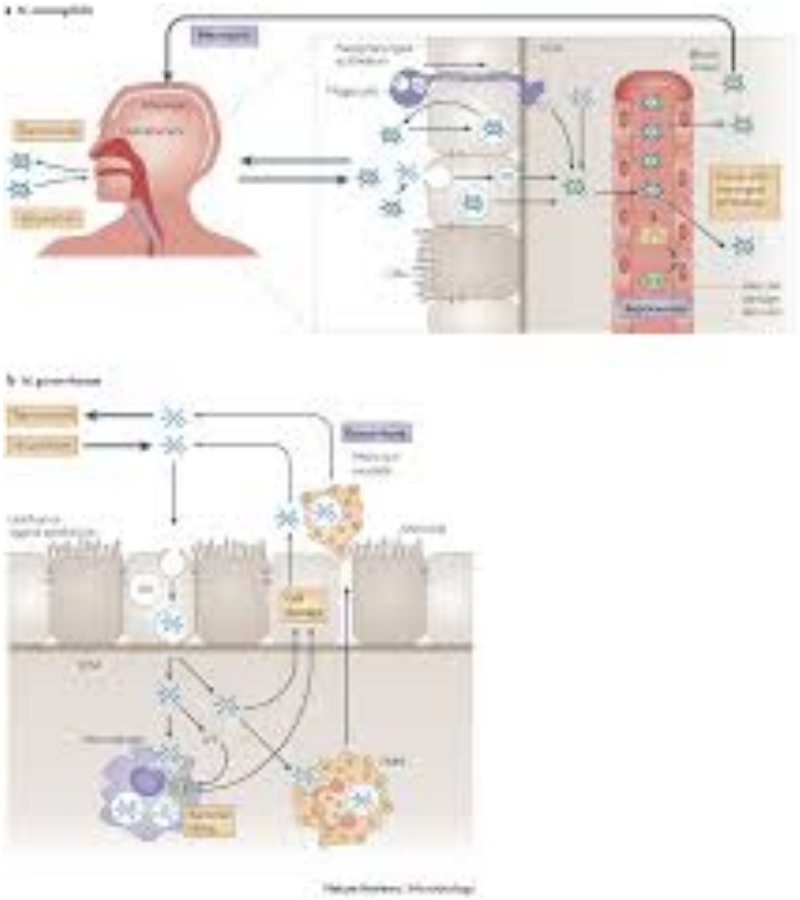


Distribution of cases of meningococcal disease per serogroup and geographical area



Meningococcal Disease Pathogenesis

- Organism colonizes **nasopharynx**
- In some persons organism enters the **bloodstream** and causes infection at distant site
- Antecedent URI may be a contributing factor

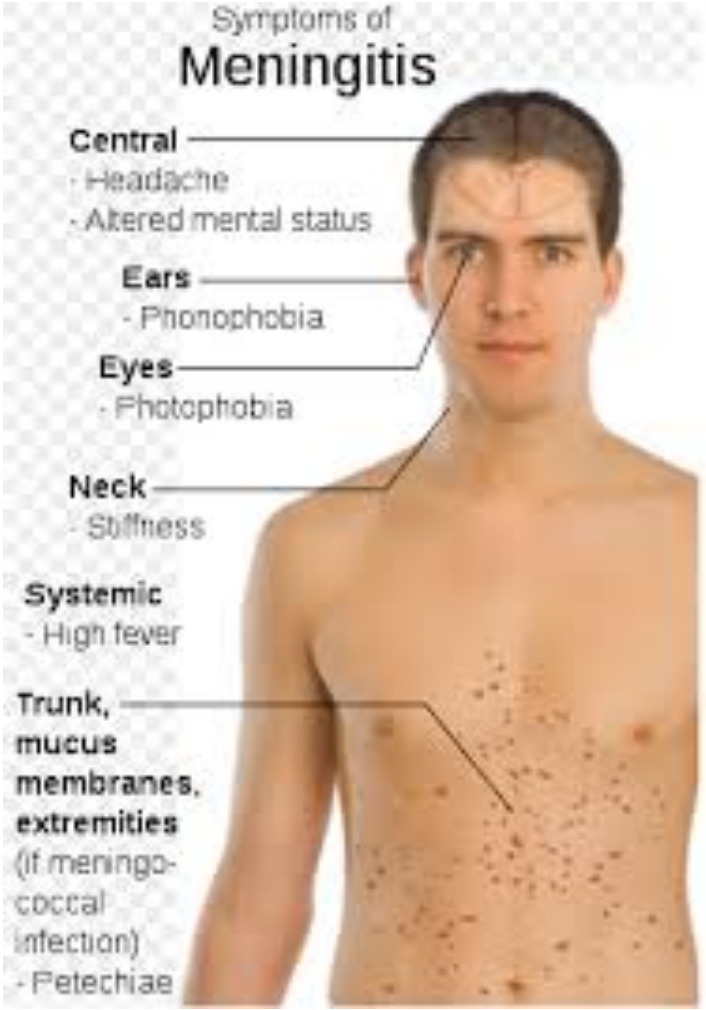


Neisseria meningitidis
Clinical Features

- **Incubation** period 3-4 days (range 2-10 days)
- Abrupt onset of fever, meningeal symptoms, hypotension, and rash
- **Fatality rate** 10%-15%, up to 40% in meningococcemia

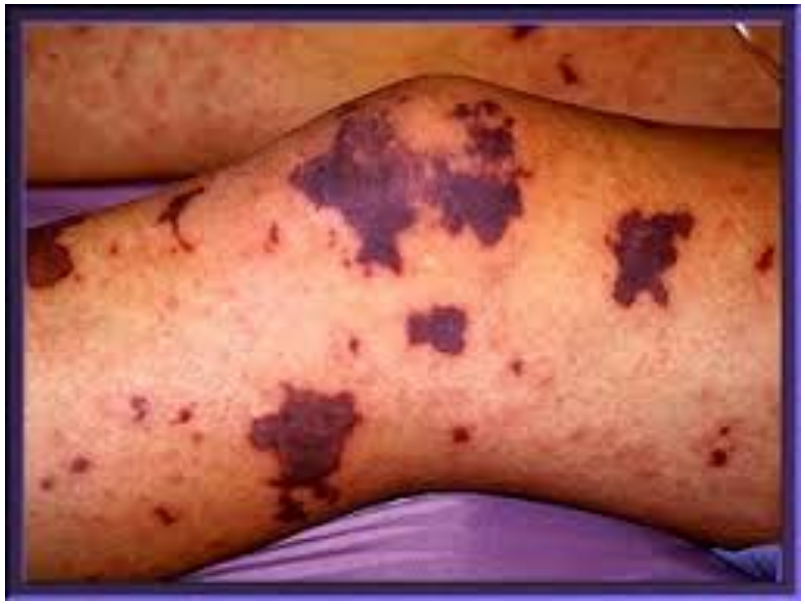
Meningococcal Meningitis

- Most common presentation of invasive disease
- Results from hematogenous dissemination
- Clinical findings fever
  - headache
  - stiff neck



Meningococcemia

- Bloodstream infection
- May occur with or without meningitis
- Clinical findings
  - fever
  - petechial or purpuric rash
  - hypotension
  - shock
  - acute adrenal hemorrhage
  - multiorgan failure



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The Signs and Symptoms of Meningitis

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Survivors Talk about Meningococcal Meningitis

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Neisseria meningitidis
Risk Factors for Invasive Disease

Host factors

- deficiencies in the terminal common complement pathway
- functional or anatomic asplenia
- certain genetic factors

Environmental factors

- antecedent viral infection
- household crowding
- active and passive smoking
- occupational (microbiologists)

Meningococcal Disease
Laboratory Diagnosis

- Bacterial culture
- Gram stain
- Non-culture methods
  - PCR
  - antigen detection in CSF
  - serology

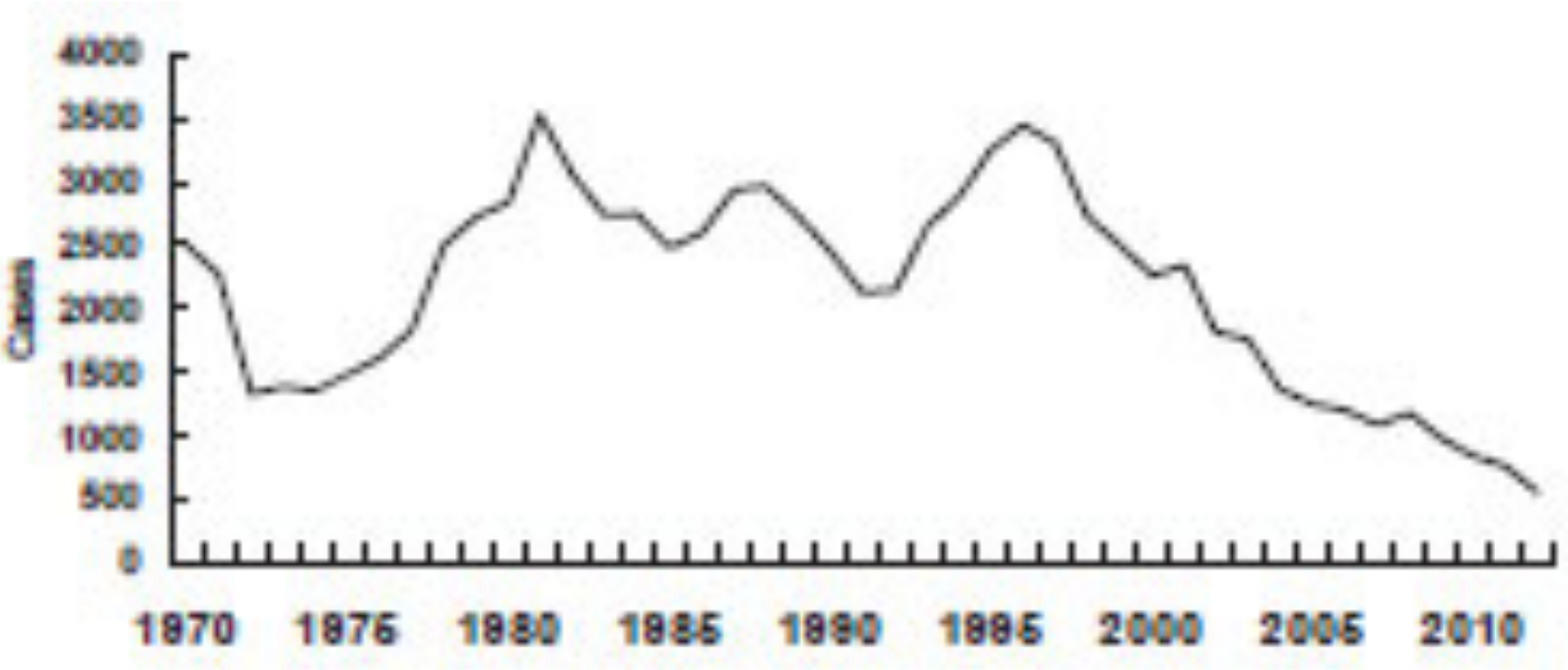
Neisseria meningitidis
Medical Management

- Empiric antibiotic treatment after appropriate cultures are obtained
- Treatment with **penicillin** alone recommended after confirmation of *N. meningitidis*

Meningococcal Disease Epidemiology

- **Reservoir**
  - Human
- **Transmission**
  - respiratory droplets
- **Temporal pattern**
  - peaks in late winter and early spring
- **Communicability generally limited**

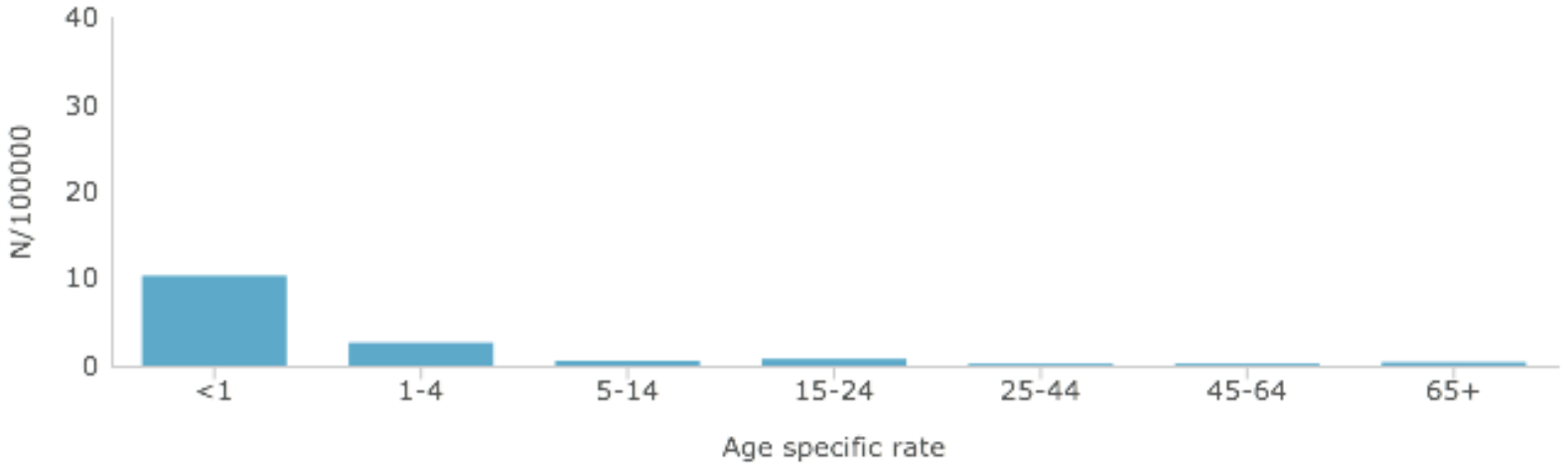
Meningococcal Disease
United States, 1972-2012



Invasive meningococcal disease
All cases - Notification rate
Europe, 2000-2014

ECDC

Invasive meningococcal disease
All cases - Notification rate per age class
Europe, 2000-2014



ECDC

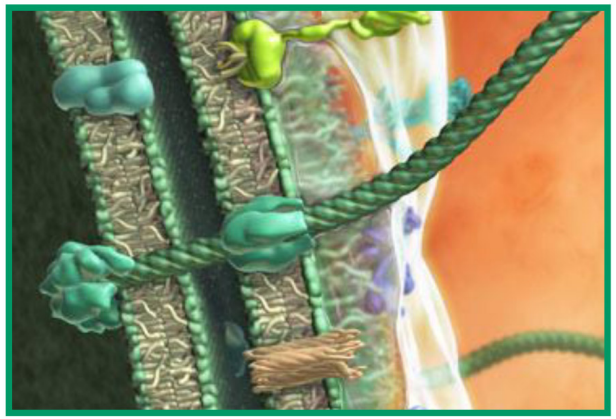
The meningitis belt

The history of anti-meningococcal vaccine

1940
1960
1980
2000
2014

Polysaccharide Vaccines era

Development of polysaccharide vaccines



Polysaccharide capsule

Stephens DS. *FEMS Microbiol Rev*. 2007; 31:3-14; 2. Daugla DM, et al. *Lancet*. 2014;383:40-47; 3. Novartis receives EU approval for Bexsero®, first vaccine to prevent the leading cause of life-threatening meningitis across Europe [press release]. Basel, Switzerland; Novartis International AG; January 22, 2013.

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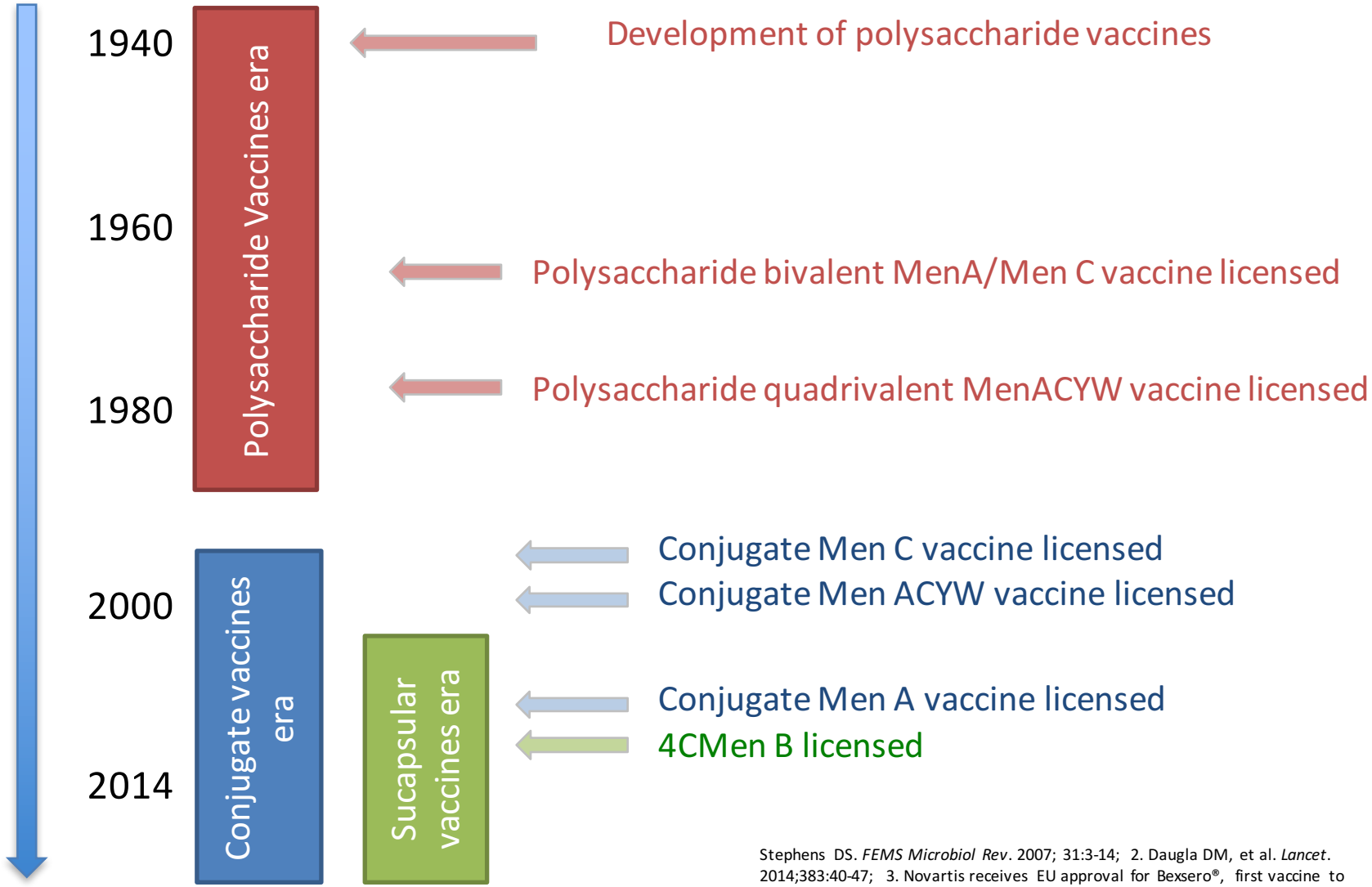
The history of anti-meningococcal vaccine



Stephens DS. *FEMS Microbiol Rev*. 2007; 31:3-14; 2. Daugla DM, et al. *Lancet*. 2014;383:40-47; 3. Novartis receives EU approval for Bexsero®, first vaccine to prevent the leading cause of life-threatening meningitis across Europe [press release]. Basel, Switzerland; Novartis International AG; January 22, 2013.

Men C CRM conjugate vaccine

- **Immunogenicity** 90-93%
- Vaccination **schedule**
  - Three doses (3, 5/6, 11/12 months of age) for subjects <1 years old
  - 1 dose for subjects aged >1 years
- Around 10% of vaccinated subjects loss immunological memory each years
- A booster dose is recommended at 5/6 years

This vaccine is currently offered to all new-borns in Italy

Meningococcal Polysaccharide Vaccine (MPSV4)

- licensed in the United States in 1974
- Quadrivalent polysaccharide vaccine (**A, C, W, Y**)
- Administered by subcutaneous injection
- 10-dose vial contains thimerosal as a preservative

Meningococcal Polysaccharide Vaccine (MPSV4)

- not effective in children younger than 18 months of age
- **poor immunogenicity in children younger than 2 years of age**
- response typical of a T-cell independent antigen
- “switching” from IgM to IgG production is poor
- **little boost in antibody titer occurs with repeated doses**

Meningococcal Polysaccharide Vaccine (MPSV4)

- Serogroups A and C
  - clinical efficacies of 85% or more among school-aged children and adults during outbreaks.
- Serogroups W and Y
  - clinical protection has not been documented
  - production of bactericidal antibodies

Meningococcal Conjugate Vaccines (MenACWY)

- licensed in 2005
- ability to elicit **immunologic memory**
- antibody persistence studies indicate that circulating antibody **declines 3 to 5 years after a single dose**

Routine MenACWY Vaccination Recommendations

- Administer either MenACWY at age **11 or 12 years** with a **booster dose at 16 years of age**
- Administer 1 dose at age 13 through 15 years if not previously vaccinated
- For persons vaccinated at age 13 through 15 years a 1-time booster dose should be administered, preferably at 16 through 18 years
- **Healthy persons who receive their first dose of meningococcal conjugate vaccine at or after age 16 years do not need a booster dose**

Routine MenACWY Vaccination Recommendations

- Routine vaccination **not recommended after age 21 years** for healthy persons who are not at increased risk of exposure
- A **booster dose is not recommended** for healthy persons **22 years of age** and older even if the first dose was administered at 11-15 years of age

High-risk Groups: Functional or Anatomic Asplenia

- **Younger than 19 months**
  - infant series at 2, 4, 6, and 12-15 months
- **19-23 months who have not received a complete series**
  - 2-dose primary series of MenACWY-CRM at least 3 months apart**
- **24 months and older who have not received a complete series 2-dose primary series of either**
  - MenACWY at least 3 months apart**

High-risk Groups: Persistent Complement Component Deficiency

- **Children 2-18 months**
  - infant series at 2, 4, 6, and 12-15 months OR 2-dose primary series of MenACWY-D starting at 9 months at least 3 months apart *
- **19-23 months without complete series of MenACWY**
  - 2-dose primary series of MenACWY at least 3 months apart*
- **24 months and older who have not received a complete series of MenACWY**
  - 2-dose primary series of either MenACWY at least 3 months apart

Additional High-risk Groups

- Meningococcal vaccination is recommended for persons at increased risk for meningococcal disease
  - microbiologists who are routinely exposed to isolates of *N. meningitidis*
  - military recruits
  - persons who travel to and U.S. citizens who reside in countries in which *N. meningitides* is hyperendemic or epidemic, particularly areas in the Sub-Saharan African "meningitis belt"
- **Revaccinate every 5 years as long as the person remains at increased risk**

High-risk Boosters

Children who receive primary immunization and remain at increased risk should receive booster doses

- if primary immunization complete by 7 years of age
  - first booster should be 3 years after primary immunization and every 5 years thereafter if at continued risk
- if primary immunization complete on or after 7 years of age
  - first booster should be 5 years after primary immunization and every 5 years thereafter if at continued risk

MenACWY and HIV Infection

- **HIV infection is not currently an indication for MenACWY vaccination**
- Some persons with HIV infection should receive MenACWY for other indications, such as adolescents or international travel
- Persons with HIV infection who are vaccinated with MenACWY should receive **2 primary series doses at least 8 weeks apart**

Meningococcal Vaccine Use in Outbreaks

Outbreak definition:

- at least 3 confirmed or probable primary cases of the same serogroup
- period of 3 months or less
- primary attack rate of more than 10 cases per 100,000 population

Both MenACWY, and MPSV4 recommended for use in control of outbreaks caused by A, C, W, and Y

MenACWY Adverse Events

- Fever
  - most frequently reported (16.8%)
- Headache (16.0%); injection-site erythema (14.6%); dizziness (13.4%)
- Syncope reported in 10%
- Serious adverse events rare death reported in 0.3%

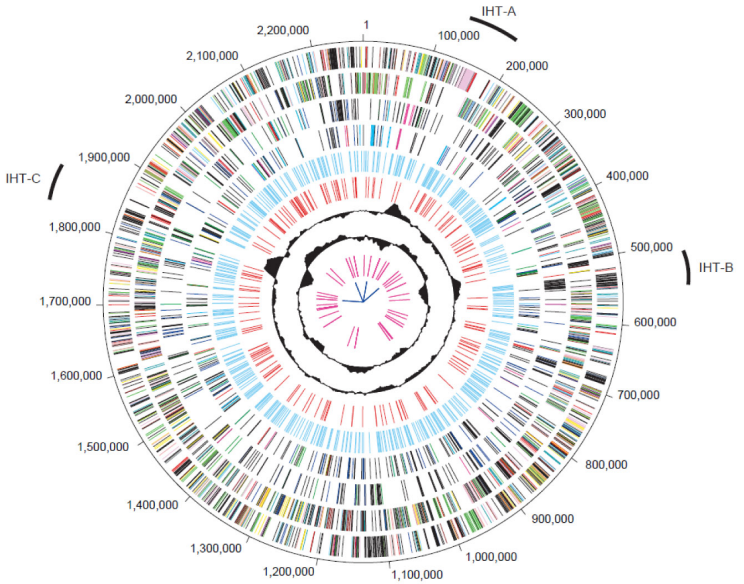
Men B vaccine

- Men B polysaccharide is similar of a neuronal components
  - Not immunogenic
  - If administered, an autoimmune reaction could be elicited
- Subcapsular proteins could be used for a Men B vaccine formulation, but they are not constantly reported in Men B

Reversse vaccinology

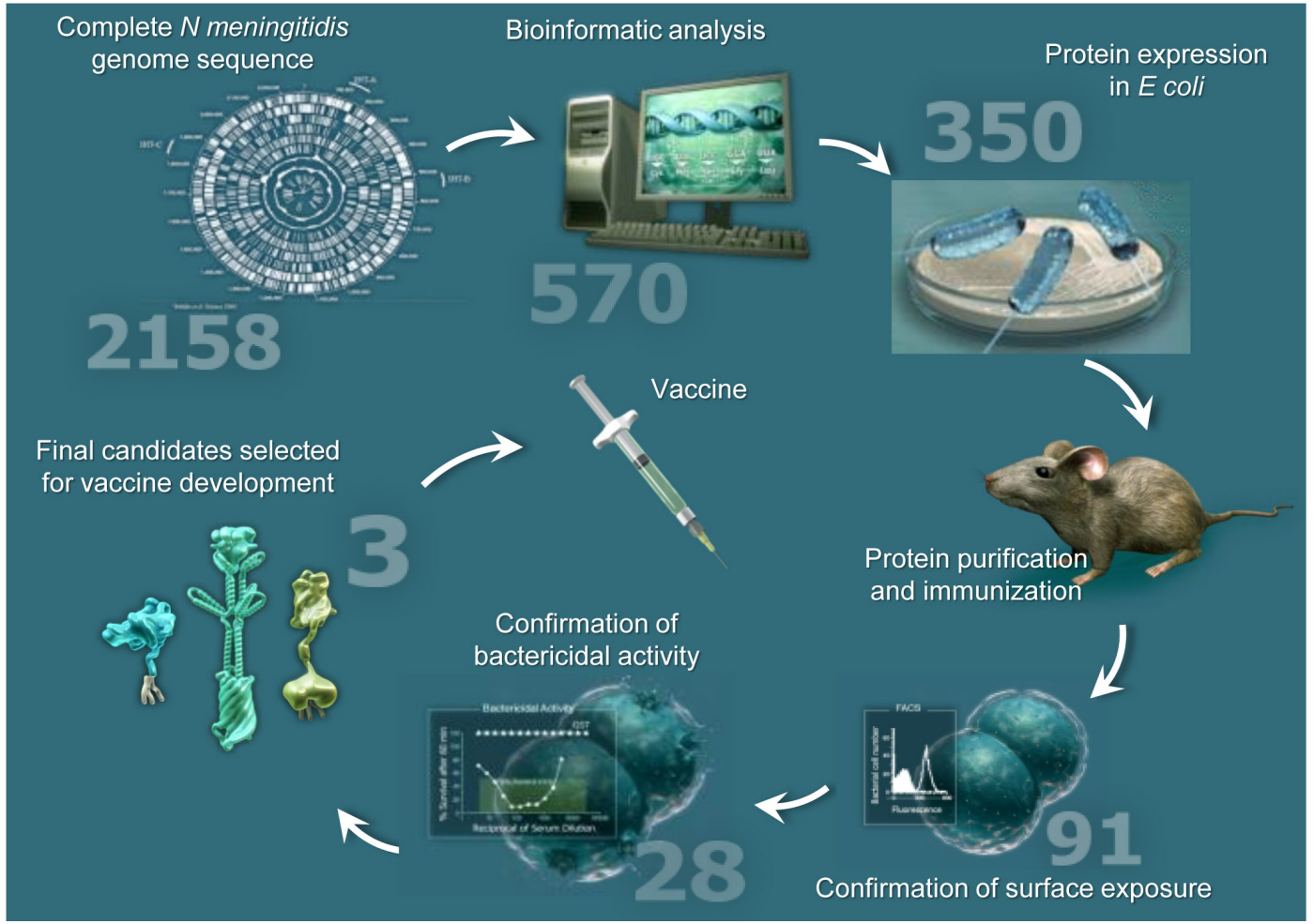
Complete Genome Sequence of *Neisseria meningitidis* Serogroup B Strain MC58

Hervé Tettelin,[1*] Nigel J. Saunders,[2] John Heidelberg,[1] Alex C. Jeffries,[2] Karen E. Nelson,[1] Jonathan A. Eisen,[1] Karen A. Ketchum,[1†] Derek W. Hood,[2] John F. Peden,[2] Robert J. Dodson,[1] William C. Nelson,[1] Michelle L. Gwinn,[1] Robert DeBoy,[1] Jeremy D. Peterson,[1] Erin K. Hickey,[1] Daniel H. Haft,[1] Steven L. Salzberg,[1] Owen White,[1] Robert D. Fleischmann,[1] Brian A. Dougherty,[1] Tanya Mason,[1] Anne Ciecko,[1] Debbie S. Parksey,[1] Eric Blair,[1] Henry Cittone,[1] Emily B. Clark,[1] Matthew D. Cotton,[1] Terry R. Utterback,[1] Hoda Khouri,[1] Haiying Qin,[1] Jessica Vamathevan,[1] John Gill,[1] Vincenzo Scarlato,[3] Vega Masignani,[3] Mariagrazia Pizza,[3] Guido Grandi,[3] Li Sun,[2] Hamilton O. Smith,[1†] Claire M. Fraser,[1] E. Richard Moxon,[2] Rino Rappuoli,[3] J. Craig Venter[1†]



Tettelin H, *et al., Science*. 2000;287:1809-1815.

Reversse vaccinology



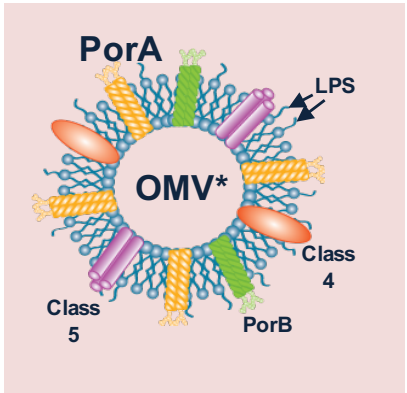
1. Tettelin H, *et al., Science*. 2000;287:1809-1815; 2. Rappuoli R. *Vaccine*. 2001;19:2688-2691; 3. Pizza M, *et al., Science*. 2000;287:1816-1820.

4C Men B components

fHbp: factor H binding protein

NHBA: Neisseria heparin–binding antigen

NadA: Neisserial adhesin A



NZ PorA P1.4: porin A*

1. Madico G, et al. *J Immunol*. 2006;177:501-510; 2. Schneider MC, et al. *Nature*. 2009;458:890-893; 3. Comanducci M, et al. *J Exp Med*. 2002;195: 1445-1454; 4. Capecchi B, et al. *Mol Microbiol*. 2005;55:687-698; 5. Mazzon C, et al. *J Immunol*. 2007;179:3904-3916; 6. Bambini S, et al. *Vaccine*. 2009;27:1794-2803; 7. Serruto D, et al. *Proc Natl Acad Sci U S A*. 2010;107:3770-3775; 8. Martin DR, et al. *Clin Vaccine Immunol*. 2006;13:486-491.

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4CMenB

Pre- marketing studies

Around 7.800 subjects received almost 1 dose of vaccine

New-borns and infats 2 months/2 years

- 5.849 received almost 1 dose
- 3.285 received the complete schedule and the booster dose

250 infants 2-10 years

1.703 adolescents (≥11 years) and adults

BEXSERO [summary of product characteristics]. Siena, Italy: Novartis Vaccines and Diagnostics S.r.l.; 2013.

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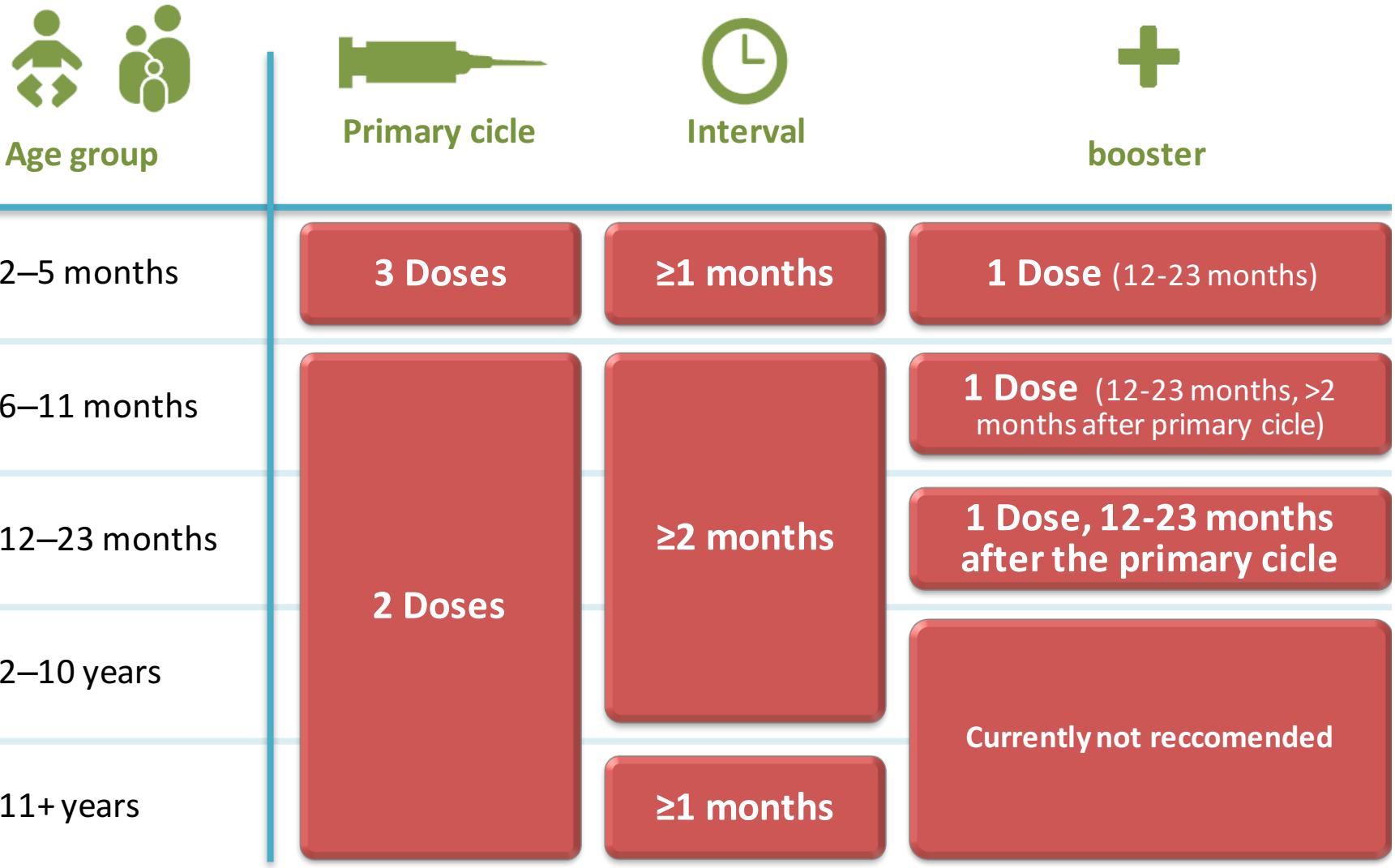
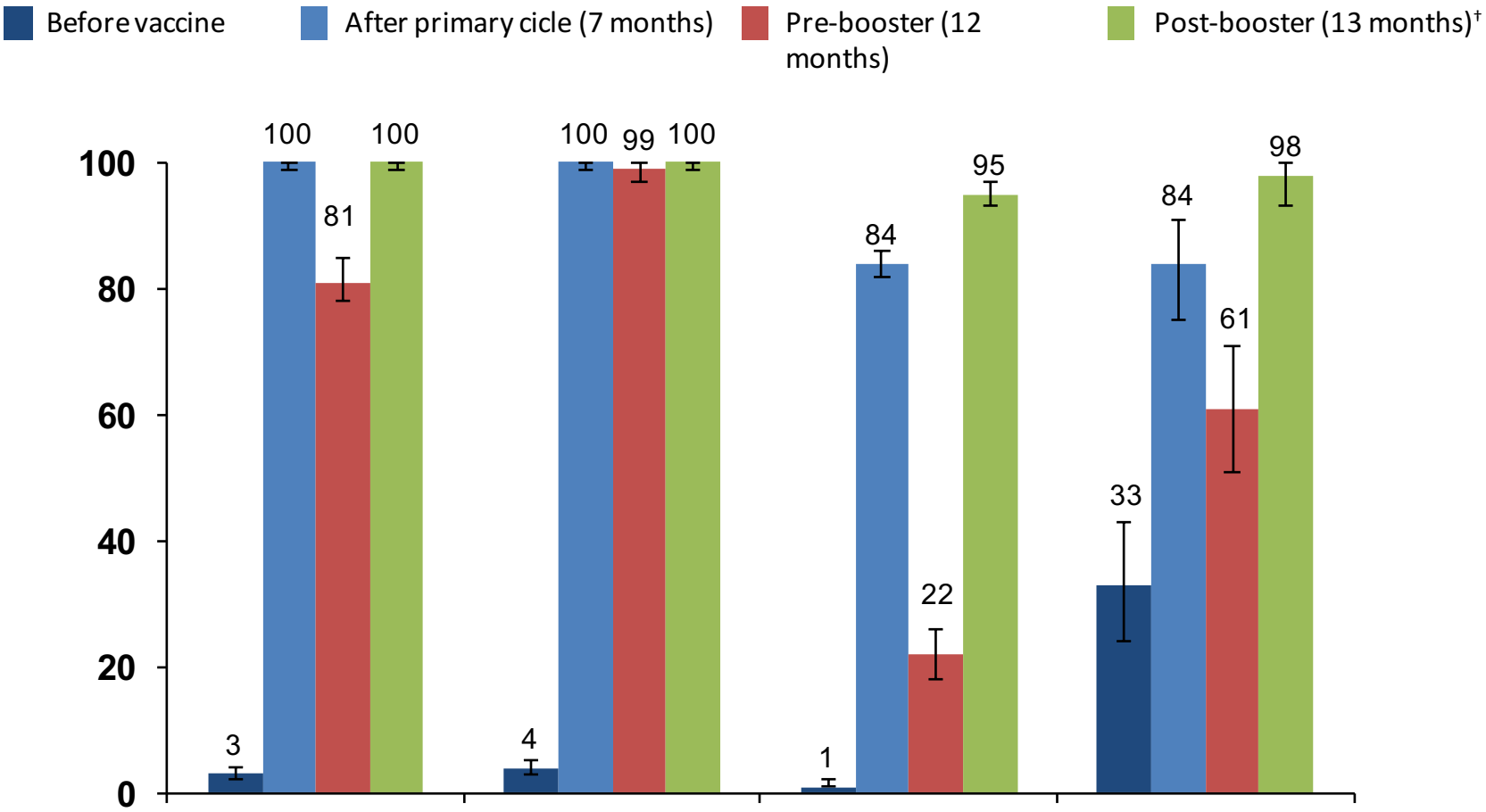
4CMenB

Vaccination schedule



4CMenB – Immunogenicity among newborns who received 3+1 schedule during the first year of life



Vesikari T, et al. *Lancet*. 2013;381:825-835.

4C Men B safety profile
Infants and children

Very common:

- fever (≥38°C)
- injection site tenderness (including severe injection site tenderness defined as crying when injected limb is moved)
- injection site erythema
- injection site swelling
- injection site induration
- irritability
- eating disorders
- sleepiness, unusual crying, headache
- diarrhoea, vomiting (uncommon after booster)
- rash (children aged 12 to 23 months) (uncommon after booster)
- arthralgia

Uncommon

- seizures (including febrile seizures)
- pallor (rare after booster)
- eczema

Rare:

- Kawasaki syndrome
- urticaria

4C Men B safety profile
Adolescents (from 11 years of age) and adults

Very common:

- injection site pain (including severe injection site pain defined as unable to perform normal daily activity)
- injection site swelling
- injection site induration
- injection site erythema
- malaise
- Headache
- Nausea
- myalgia
- arthralgia

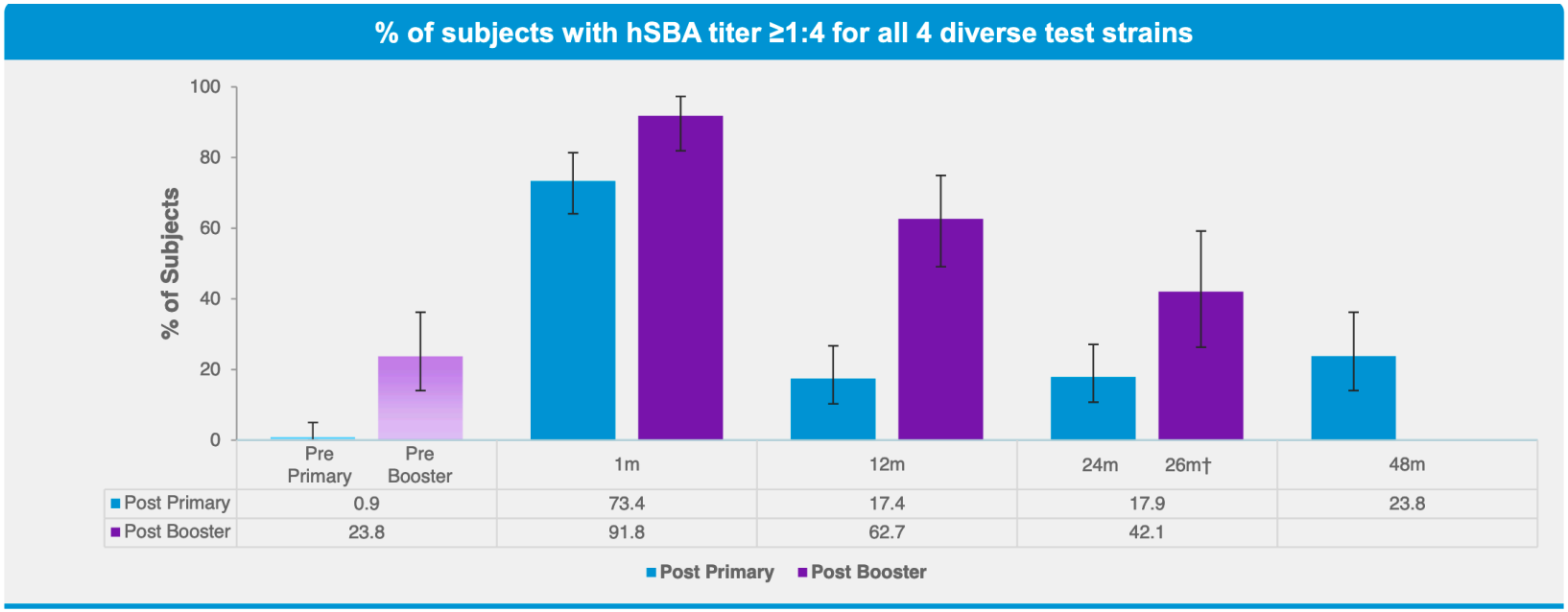
FHBP Men B Vaccine

- Pfizer's MenB vaccine is based on a surface-exposed factor H binding protein (FHbp)
- Expressed in > 95% of invasive MenB strains
- FHbp sequences segregate into two genetically and immunologically distinct subfamilies, A and B
- MenB-FHbp contains two lipidated FHbp variants (A05 and B01), one from each sub

FHBP Men B Vaccine

- MenB-FHbp (Trumenba) is a 2- or 3-dose vaccine indicated for the prevention of invasive meningococcal disease caused by serogroup B
- Healthy Adolescents should receive 2 doses of MenB-FHbp, administered at 0 and 6 months
- For persons at increased risk for meningococcal disease and for use during serogroup B disease outbreaks, 3 doses of MenB-FHbp should be administered at 0, 1–2, and 6 months

Immunogenicity of FHBP Men B vaccine



Safety of FHBP Men B vaccine

- Pain at the injection site was the most commonly reported local reaction, reported by **84.4%** to **93.5%** of subjects
- Fatigue (**51.9%** to **65.6%**) and headache (**37.5%** to **56.3%**) were the most commonly reported systemic events
- **3.7%** to **12.5%** of subjects reported ≥1 AE
  - 3 subjects reported related AEs
    - Mild worsening of psoriasis (0,6m Group)
    - Influenza like illness, classified as a SAE (0,2m Group)
    - Moderate dizziness (0,2,6m Group)
- No reported SAEs during persistence phase post booster (up to 26m)

Meningococcal diseases
Indications for Chemoprophylaxis

- Household members
- Child care center contacts
- Anyone directly exposed to the patient's oral secretions in 7 days before symptom onset
- Travelers with direct contact with respiratory secretions from an index patient or for anyone seated directly next to an index patient on a prolonged flight (more than 8 hours)

Timing of Chemoprophylaxis

- Should be administered as soon as possible, ideally **less than 24 hours after identification of the index patient**
- Chemoprophylaxis administered more than 14 days after onset of illness in the index patient probably of limited or no value

Antimicrobials

- Rifampin
- Ciprofloxacin
- Ceftriaxone

90%-95% effective in reducing nasopharyngeal carriage of N. meningitidis