



# Meningococcal Disease in Patients Receiving Eculizumab in the United States

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# Outline

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  - Meningococcal disease
  - Eculizumab
    - Risk of meningococcal disease
- Case report
- Responses to Epi-X call for cases
- In vitro data
- Summary
- Discussion

**Background**

# Meningococcal Disease

- Meningitis and/or bloodstream infection
- Signs and symptoms:
  - Fever, headache, stiff neck, confusion, rash
- Rapid onset and progression in previously healthy people
- 10-20% of patients die even with appropriate treatment
- 11-19% of survivors have long-term health issues



# Eculizumab (Soliris<sup>®</sup>, Alexion pharmaceuticals)

- Complement component inhibitor licensed in the US for treatment of two rare, life-threatening illnesses:
  - Paroxysmal nocturnal hemoglobinuria (PNH) (2007)
    - Lifelong eculizumab treatment expected
  - Atypical hemolytic uremic syndrome (aHUS) (2011)
    - Optimal treatment duration not clear – may be lifelong for some patients but shorter for others<sup>1</sup>
  - Both have annual incidence of ~0.1–0.2/100,000<sup>2,3</sup>
- FDA-approved prescribing information includes a Black Box Warning for increased risk of meningococcal disease in recipients

# Eculizumab and Meningococcal Disease

- Data from the manufacturer<sup>1</sup>:
  - 16 meningococcal disease cases (1 death) out of 5207 person-years of eculizumab exposure during 2007–2014
    - Age range: 17–45 years
    - All received meningococcal vaccination
    - 1 serogroup B, 2 serogroup C, 2 serogroup Y, 11 unknown serogroup
  - Incidence of 307 per 100,000 person-years
    - 1000–2000 times greater than baseline risk for healthy individuals

# Risk Evaluation and Mitigation Strategy (REMS)

- Program required by FDA to manage known or potential serious risks associated with a drug product
- Soliris<sup>®</sup> (eculizumab) REMS purpose: mitigate the occurrence and morbidity associated with meningococcal infections by informing healthcare providers and patients about the:
  - Increased risk for meningococcal infections with Soliris<sup>®</sup>
  - Early signs of invasive meningococcal infections, and
  - Need for immediate medical evaluation of signs and symptoms consistent with possible meningococcal infections

# Soliris® REMS Elements

- Patient Medication Guide
- Patient Safety Information Card
- Prescriber certification – providers agree to:
  - Counsel patients and provide the patient educational materials
  - Provide the Medication Guide to patients prior to each infusion
  - Review the educational materials and product labeling and comply with directions for safe use
    - Ensure patients receive a meningococcal vaccine
  - Promptly report meningococcal disease cases to FDA or Alexion
- Assessments submitted to FDA every two years

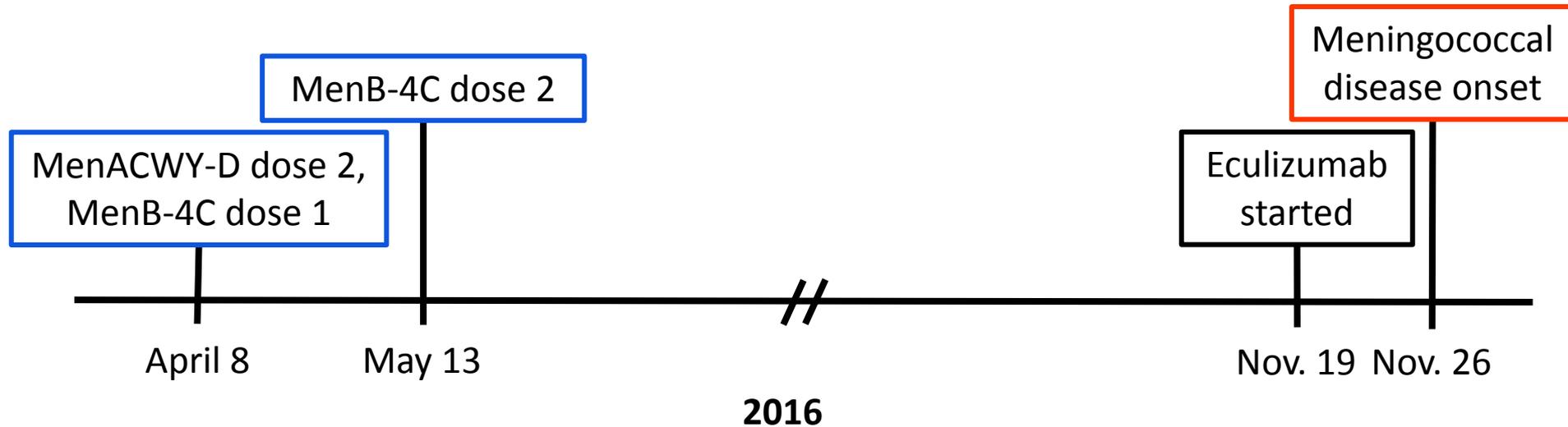
# Vaccination Recommendations for Eculizumab Recipients

- Should receive both serogroup ACWY (MenACWY)<sup>1</sup> and serogroup B (MenB)<sup>2</sup> meningococcal vaccines
- Eculizumab product insert<sup>3</sup>:
  - Meningococcal vaccination should be administered at least 2 weeks prior to initiating eculizumab
  - If treatment is initiated within 2 weeks of vaccination, antibiotic prophylaxis usually provided until at least 2 weeks after vaccination
  - “Benefits and risks of antibiotic prophylaxis...have not been established”

**Case Report**eport

# Case Report

- Fatal meningococcal disease case in a 16 year old girl with paroxysmal nocturnal hemoglobinuria (PNH) on eculizumab
- Initially reported as serogroup B

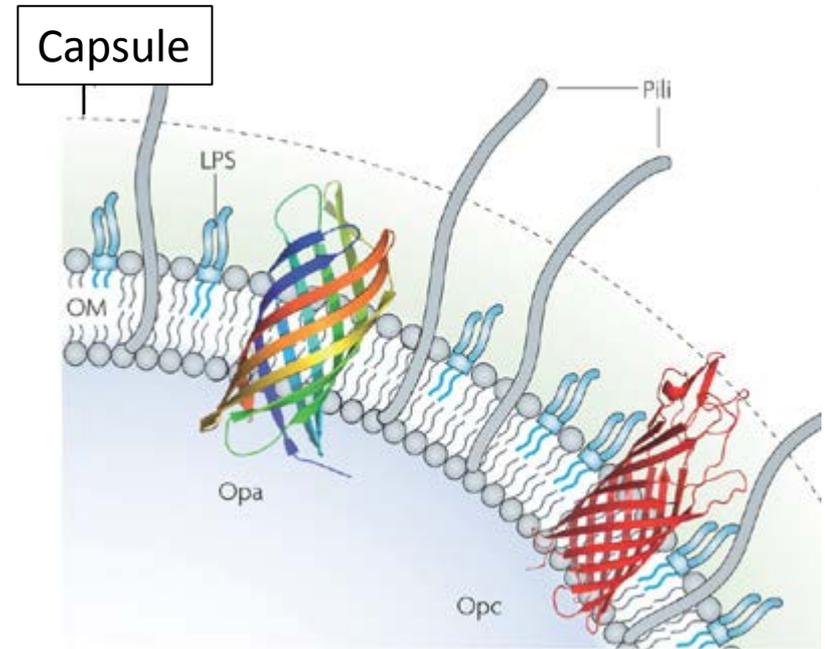


# Case Report: Isolate Characterization at CDC

- Testing at CDC showed strain actually nongroupable (NG)

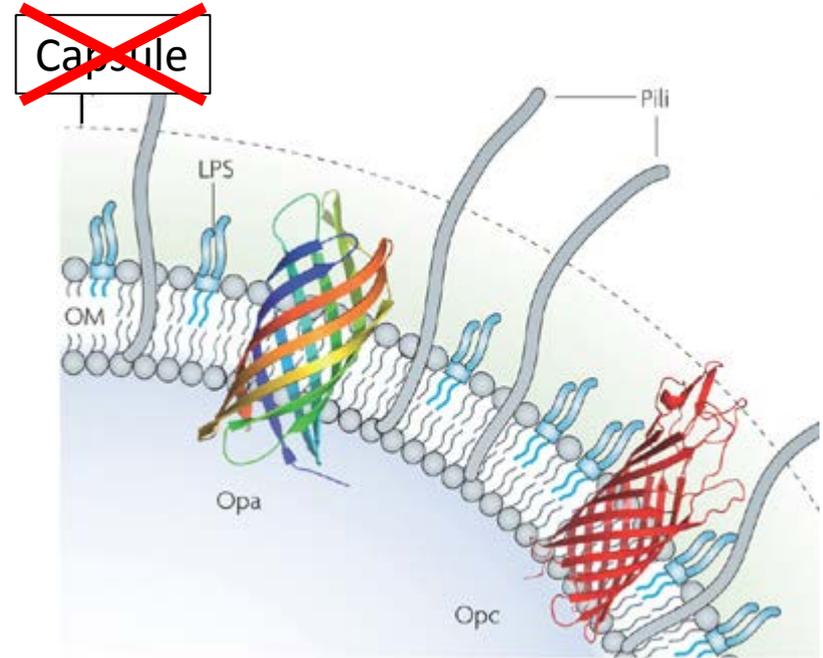
# Meningococcal Serogroups

- Classified into serogroups based on capsule
- 12 serogroups
  - A, B, C, W, X, and Y primary causes of disease



# Nongroupable *N. meningitidis*

- Nongroupable: no capsule expression
- Two reasons an isolate can be classified as nongroupable:
  - May have capsule gene but not currently expressing
  - May lack capsule gene: incapable of expressing polysaccharide capsule
    - Rarely cause invasive disease
- Asymptomatic carriage is common
  - 10-24% in recent US carriage evaluations in college students<sup>1,2</sup>



# Case Report: Isolate Characterization at CDC

- Testing at CDC showed strain actually nongroupable (NG) by:
  - Slide agglutination (SASG)
  - Polymerase chain reaction (PCR)
  - Whole genome sequencing (WGS)
    - WGS demonstrated complete absence of capsule gene
- Isolate sequence type (ST-2578) more commonly associated with asymptomatic carriage rather than invasive disease

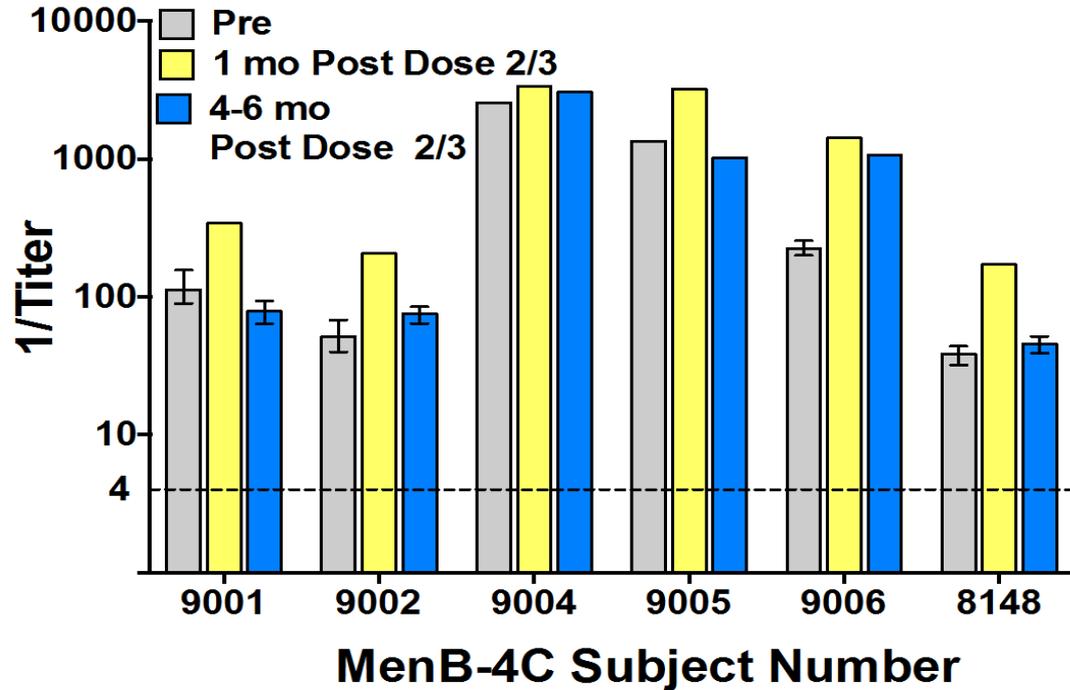
# Case Report: Vaccine Antigen Characterization

- MenACWY vaccines do not protect against nongroupable meningococci
- MenB vaccine proteins are not serogroup-specific
  - MenB vaccine cross-protection for nongroupable meningococci has not been assessed
- Antigen sequencing results for the MenB-4C (Bexsero<sup>®</sup>) vaccine antigens in the case isolate:
  - FHbp ID 100 (sub-family B) – 98% similar to the one in MenB-4C
  - NhbA peptide 2 – same as MenB-4C
  - No NadA; PorA does not match PorA in MenB-4C
- High expression of FHbp and NhbA by flow cytometry<sup>1</sup>

# Serum Bactericidal Responses to Case ST-2578 NG Strain in Serum from Healthy Adults Immunized with 2 or 3 Doses of MenB-4C

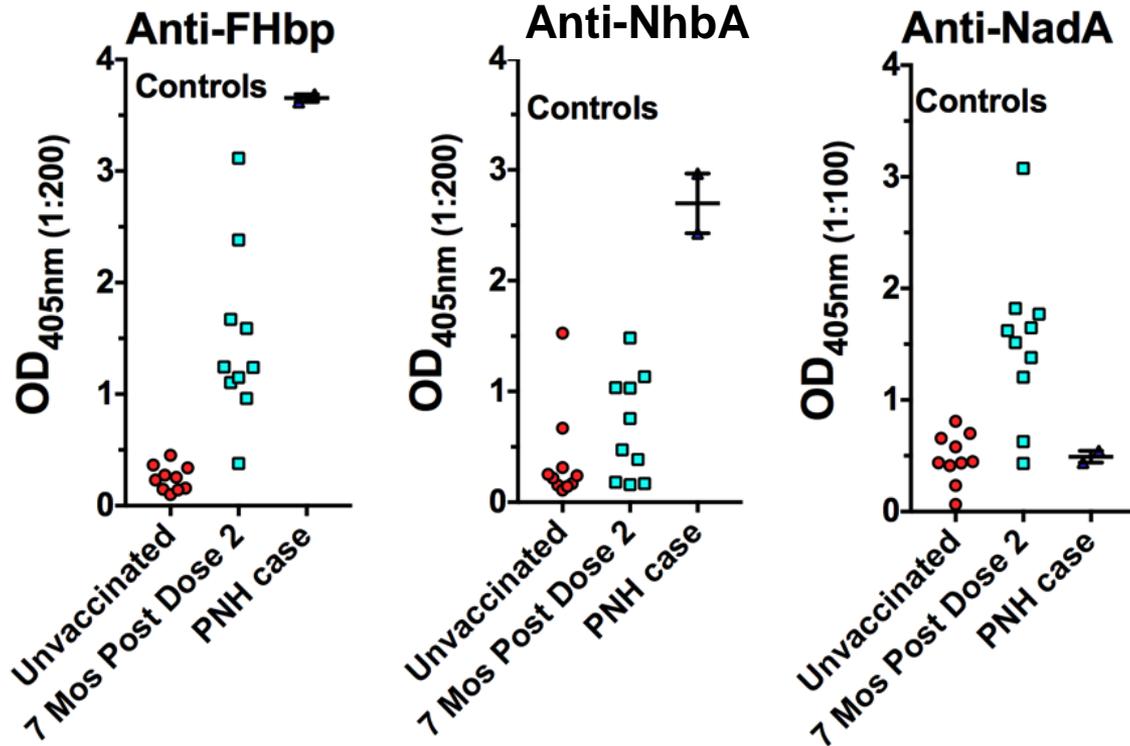
- Serum bactericidal activity assessed using serum from 6 healthy adults
- Three time points:
  - Before MenB-4C vaccination
  - 1 month after receiving 2–3 doses MenB-4C
  - 4–6 months after receiving 2–3 doses MenB-4C

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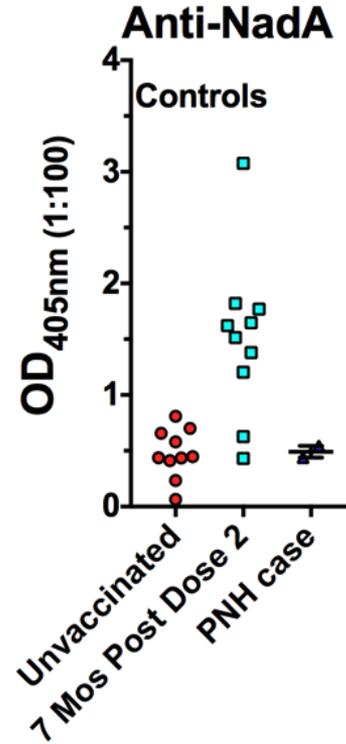
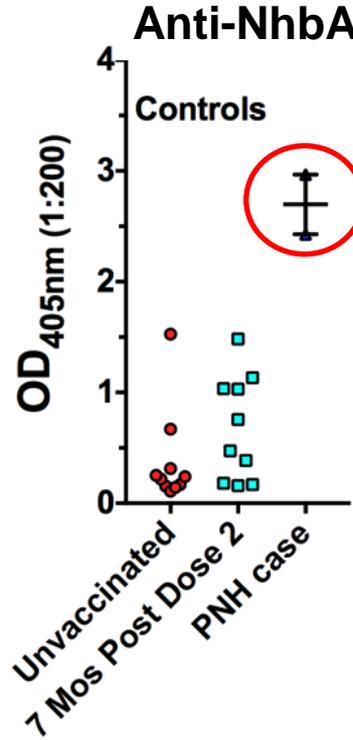
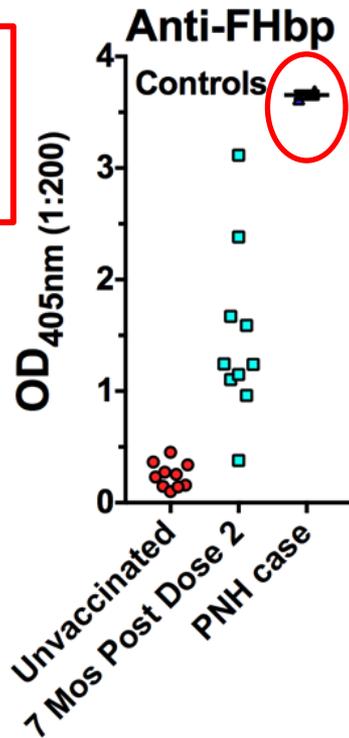
All 6 adults had **pre-immunization** SBA titers >1:16

# Case Report: Post-Mortem Serum IgG Antibody Reactivity to MenB Vaccine Antigens



# Case Report: Post-Mortem Serum IgG Antibody Reactivity to MenB Vaccine Antigens

High antibody titer to FHbp and NHba



# Case Report Summary

- Fatal meningococcal disease case in adolescent treated with eculizumab
- Patient vaccinated with MenACWY and MenB vaccines ~6 months before disease onset
- Strain NG by SASG, PCR, and WGS
- MenB-4C expected to provide protection against this strain based on antigen typing
- Serum from 6 healthy adults (pre- or post-vaccination) easily killed this strain
- Patient died despite apparently strong memory antibody response to strain
- **Normally nonpathogenic strain caused fatal illness despite vaccination**

**Epi-X Call for Cases**

# Epi-X: Call for Cases: Meningococcal Disease in Patients Receiving Eculizumab – 2007–Present

- Epi-X: CDC web-based communications platform to share and request preliminary health surveillance information
- Requested health departments review existing case investigation records to identify meningococcal disease cases in eculizumab recipients since 2007
- Epi-X posted 2/3/17; follow-up via multiple emails

# Epi-X: Initial Responses

- Responses received from 46 jurisdictions<sup>1</sup>
- 16 cases identified from 10 jurisdictions
- Median age: 30 (range: 16-83)
  - Indication for eculizumab:
    - 10 PNH
    - 5 aHUS
    - 1 Devic's Disease (neuromyelitis optica – enrolled in clinical trial)

<sup>1</sup>Information pending from: ID, MD, MS, NE, NM, WV

# Epi-X: Illness presentation and severity

- Presentation
  - 16/16 with bloodstream infection
  - 6/16 with meningitis
- All patients hospitalized
  - Mean 6.6 days, range 1–14
- 1 fatality

# Epi-X: Initial Responses - Serogroups

Serogroup (SASG)	Serogroup (PCR)	N cases
NG	NG	4
Unknown	NG	1
NG	B	2
NG	C	1
NG	Y	3
Y	Y	4
Unknown	Unknown	1

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5 NG by PCR

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6 more NG by SASG

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NG	Y	3
Y	Y	4
Unknown	Unknown	1

**3/6 have clear defects identified by WGS**

# Epi-X: Initial Responses – Vaccination Status

- Not all patients received recommended vaccinations:
  - 9/15 (60%) with known vaccination status received MenACWY<sup>1</sup> vaccine before onset
  - 3/7 (43%) with disease onset in 2015–2016 received MenB vaccine before onset
    - 2 with complete series, 1 with 1 dose

<sup>1</sup>Vaccine type not specified for one patient, but received prior to MenB vaccine licensure

# Epi-X: Initial Responses – Vaccination Status

- Vaccine failures
  - 2/4 (50%) of serogroup Y (SASG) cases in patients with documented prior MenACWY vaccination
  - Consistent with data from manufacturer<sup>1</sup> and prior reports<sup>2</sup>
- 1 patient receiving prophylactic penicillin at time of disease onset
  - Reported poor compliance

<sup>1</sup><http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM423031.pdf> <sup>2</sup>Cullinan et al. 2015; Pediatrics 135(6):e1506-9

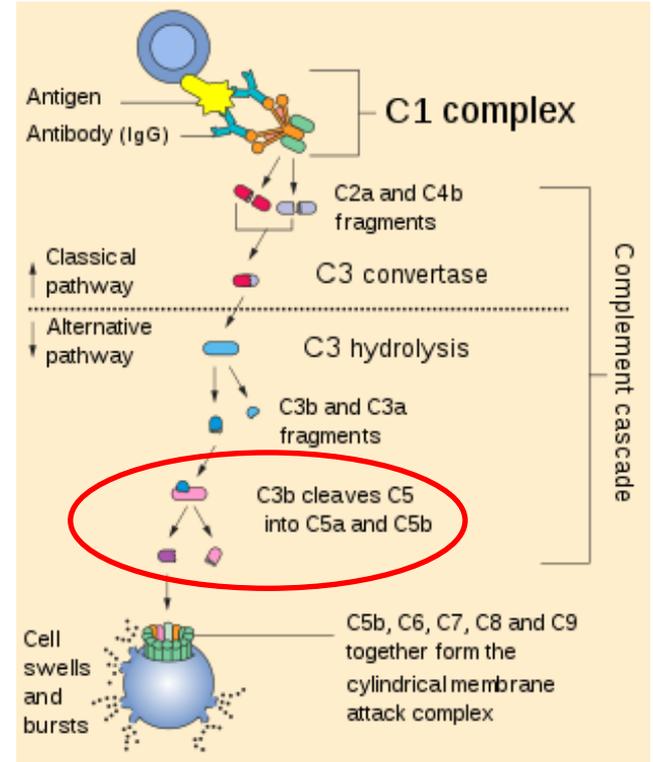
## Epi-X: Summary

- At least 8 of 16 cases (50%) due to NG strains
  - 5 NG by PCR
  - 3 more NG by SASG with capsule operon defect identified by WGS
- 40% of cases with known MenACWY vaccination status and 57% of cases with known MenB vaccination status (2015–2016) had not been vaccinated prior to disease onset
  - Routine case investigations may not capture full vaccination history
- 2/4 (50%) of serogroup Y (SASG) cases occurred in persons with prior MenACWY vaccination
- **Vaccination provides incomplete protection to eculizumab recipients**

# Laboratory Data

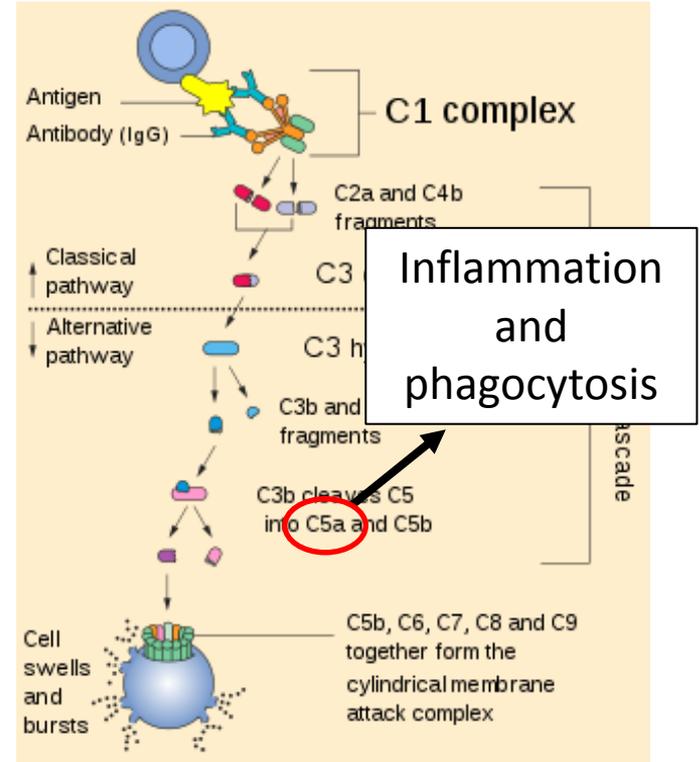
# Laboratory studies of Eculizumab

- Eculizumab blocks cleavage of C5 into C5a and C5b
- C5b needed for membrane attack complex → SBA
- **Without SBA, opsonophagocytosis needed for meningococcal killing**



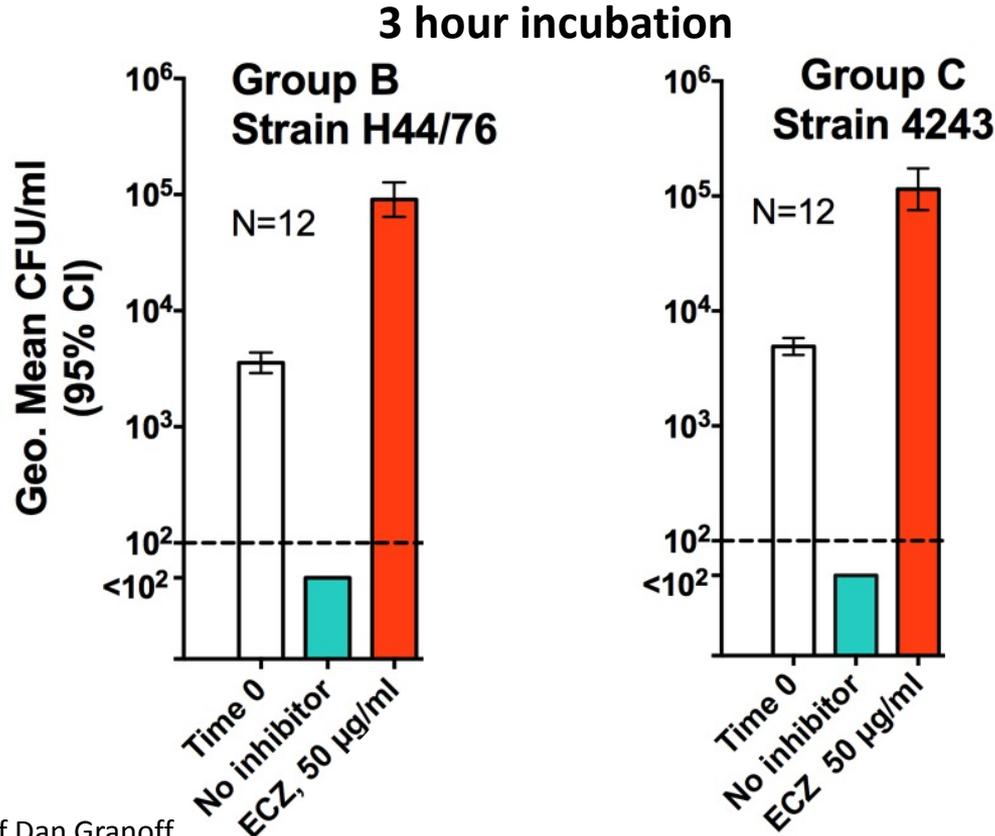
# Laboratory studies of Eculizumab

- Eculizumab blocks cleavage of C5 into C5a and C5b
- C5b needed for membrane attack complex → SBA
- **C5a promotes inflammation and phagocytosis**
- Question: does eculizumab inhibit opsonophagocytosis as well as SBA?



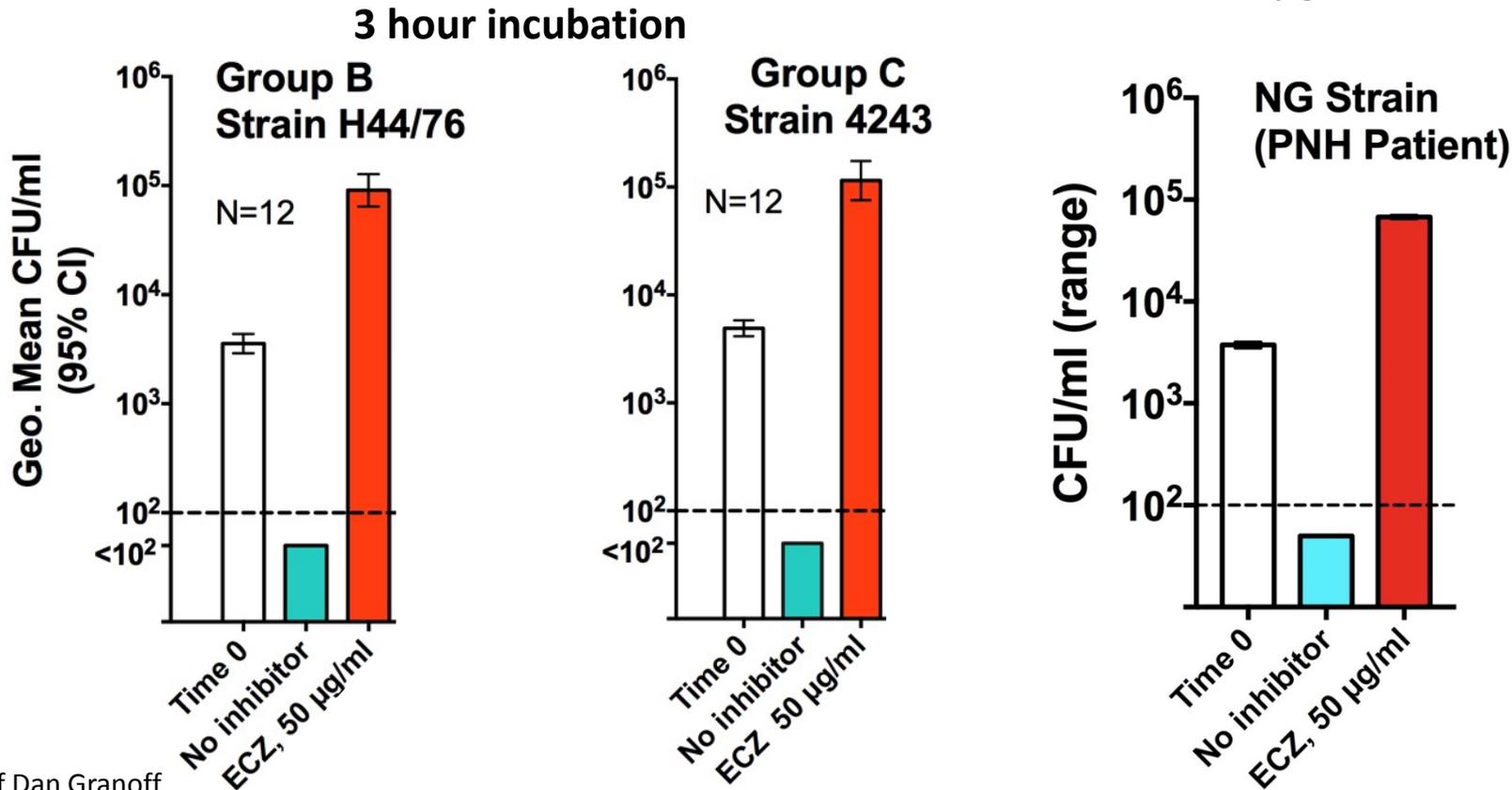
# Effect of Eculizumab on Killing of Meningococci by Anticoagulated Whole Blood from Healthy Vaccinated\* Adults

\*Vaccinated with MenACWY conjugate and MenB vaccines



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# Summary and Discussion

# Summary

- Eculizumab associated with 1000–2000x increased incidence of meningococcal disease
- Numerous meningococcal disease cases in eculizumab recipients due to nongroupable *N. meningitidis*
  - Usually commensals that rarely cause disease
  - No protection from MenACWY; protection with MenB vaccines unknown
- Breakthrough cases in spite of vaccination for appropriate serogroup (MenACWY<sup>1,2</sup> or MenB<sup>3,4</sup>)
- In vitro eculizumab blocks whole blood killing
  - Opsonophagocytosis blocked or inadequate for meningococcal killing

<sup>1</sup><http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM423031.pdf> <sup>2</sup>Cullinan et al. 2015; Pediatrics 135(6):e1506-9 <sup>3</sup>Real et al. 2017 Enferm Infecc Microbiol Clin 35(3):200-201 <sup>4</sup>Parikh et al. IPNC 2016 abstract, available at: <http://www.ipnc2016.org/>

# Concerns

- Patients on eculizumab are at risk of meningococcal disease due to strains that do not normally cause disease but are frequently carried asymptotically in the nasopharynx
- Vaccination offers limited or possibly no protection against meningococcal disease for patients on eculizumab

# Role for antibiotic chemoprophylaxis?

- Some countries recommend antibiotic prophylaxis for duration of eculizumab treatment
  - UK: “Patients are...advised to take daily prophylactic antibiotics, either penicillin...or erythromycin...”<sup>1</sup>
  - France: Continuous antibiotic chemoprophylaxis recommended until 60 days after stopping eculizumab treatment<sup>2</sup>
- Some individual providers choose to recommend for some or all patients
- No official guidance in US

<sup>1</sup><http://www.pnhleeds.co.uk/professionals/meningococcal-infection-and-eculizumab/> <sup>2</sup>Zuber et al. 2012 Nat Rev Nephrol 8(11):643-57, <http://www.hcsp.fr/Explore.cgi/avisrapportsdomaine?clefr=447>

# Role for antibiotic chemoprophylaxis?

- Penicillin most commonly used for long-term prophylaxis for eculizumab recipients
- Limited data on efficacy
- Penicillin intermediate susceptibility and resistance
  - Reports of breakthrough cases with intermediate penicillin susceptibility or resistance among eculizumab recipients<sup>1,2</sup>
  - US: 10–37% of invasive meningococcal disease isolates have intermediate susceptibility to penicillin<sup>3,4</sup>
    - Resistance remains rare (~1%)
    - Europe: 33–38% intermediate susceptibility, 0–8% resistance<sup>5-7</sup>

# Role for antibiotic chemoprophylaxis?

- Long-term penicillin therapy generally considered safe<sup>1</sup>
  - Used for long-term prophylaxis for rheumatic fever, *Streptococcus pneumoniae* infection in asplenic children<sup>2</sup>

<sup>1</sup><https://www.fda.gov/drugs/emergencypreparedness/bioterrorismdrugpreparedness/ucm072755.htm> <sup>2</sup>Enzler et al. 2011, Mayo Clin Proc 86(7):686-701

# Discussion

- Should antibiotic chemoprophylaxis be recommended for eculizumab recipients in the US?
  - Penicillin?
  - For all patients or for:
    - Those with time-limited course of treatment
      - aHUS may have shorter course of treatment vs. PNH (life-long)
    - Higher risk age groups
      - Data not available for eculizumab recipients
      - In general population: infants, adolescents, older adults
- Not anticipating ACIP vote on this topic but appreciate input from ACIP members

For more information, contact CDC  
1-800-CDC-INFO (232-4636)  
TTY: 1-888-232-6348 [www.cdc.gov](http://www.cdc.gov)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

