The new generation of complement inhibitors and implications for clinical practice and vaccination policy

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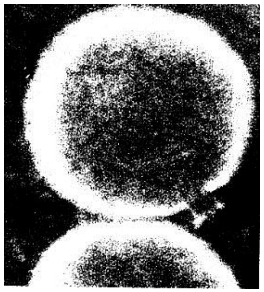
London MRF Meeting
06/11/2019

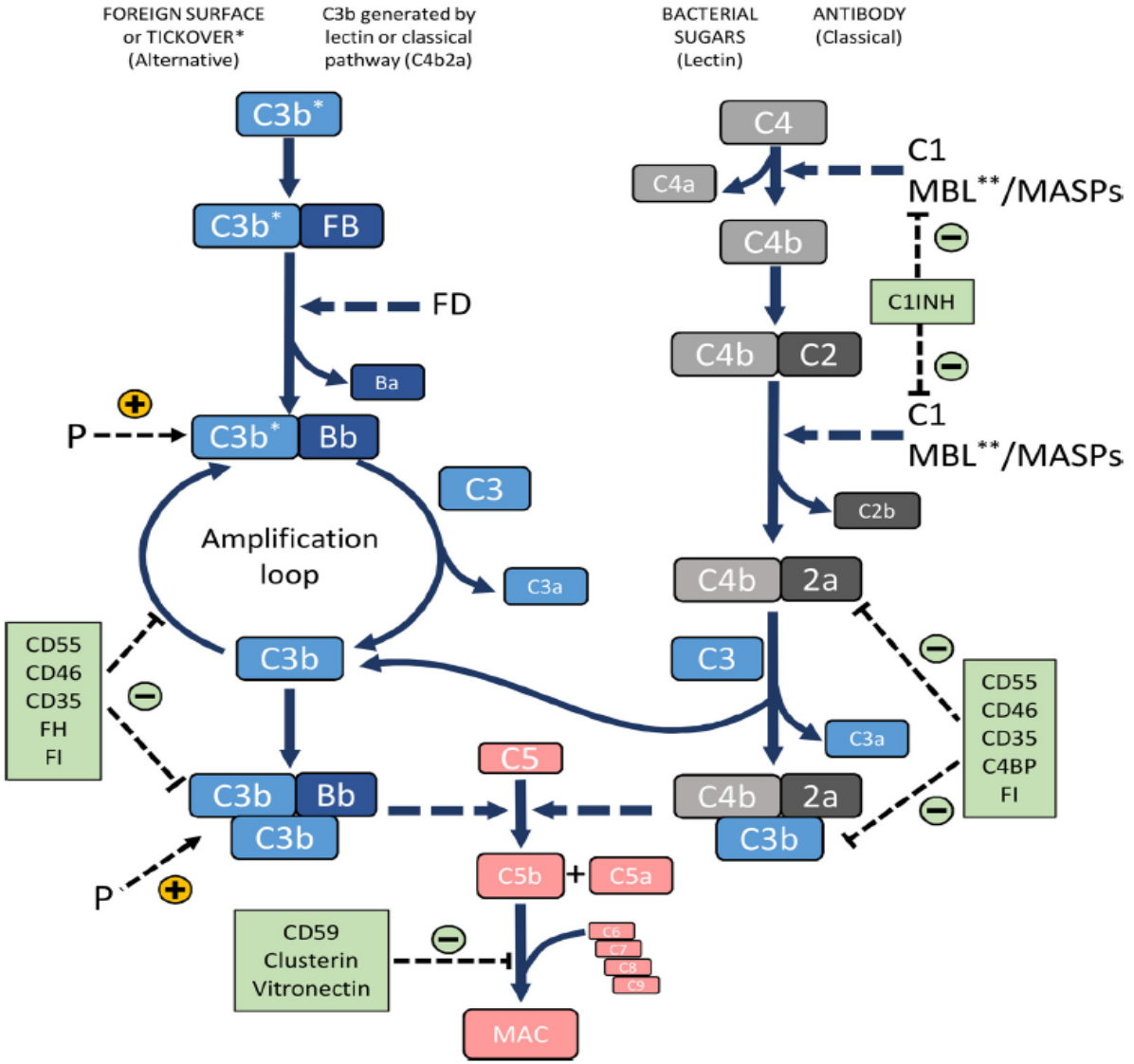
FOR RESEARCH, FOR HEALTH,
FOR OUR FUTURE

Institut Pasteur

Activation of the complement

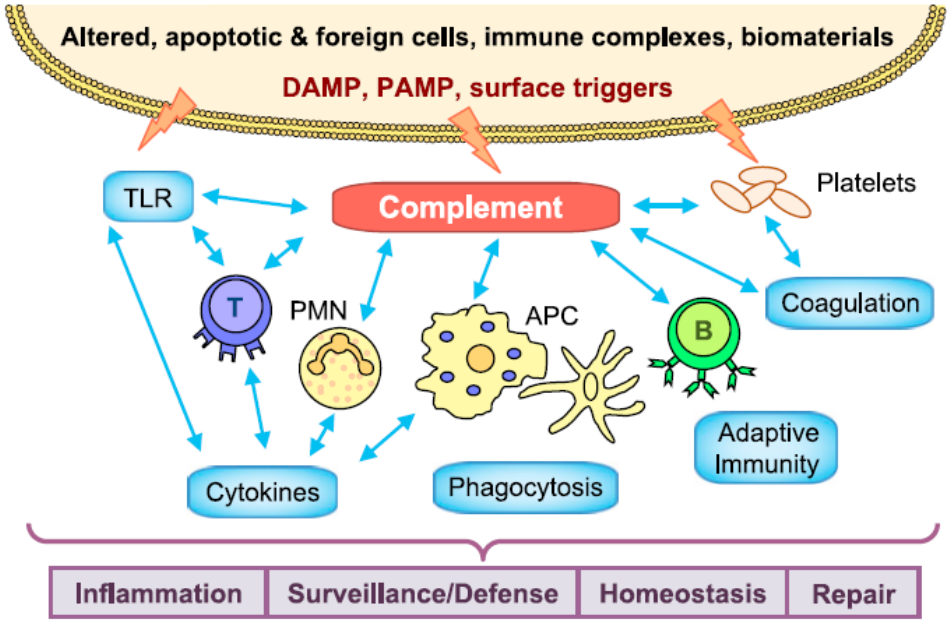
- Humoral innate immunity system
- Acute-phase proteins
-19 plasma and at least 9 membrane proteins

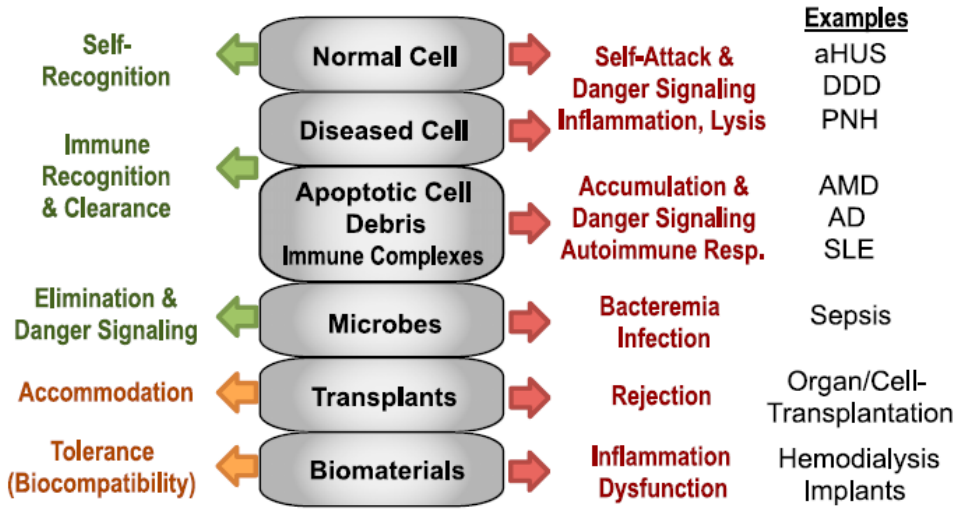




Harris et al., Molecular Immunology 102 (2018) 89–119

Complement pathophysiology



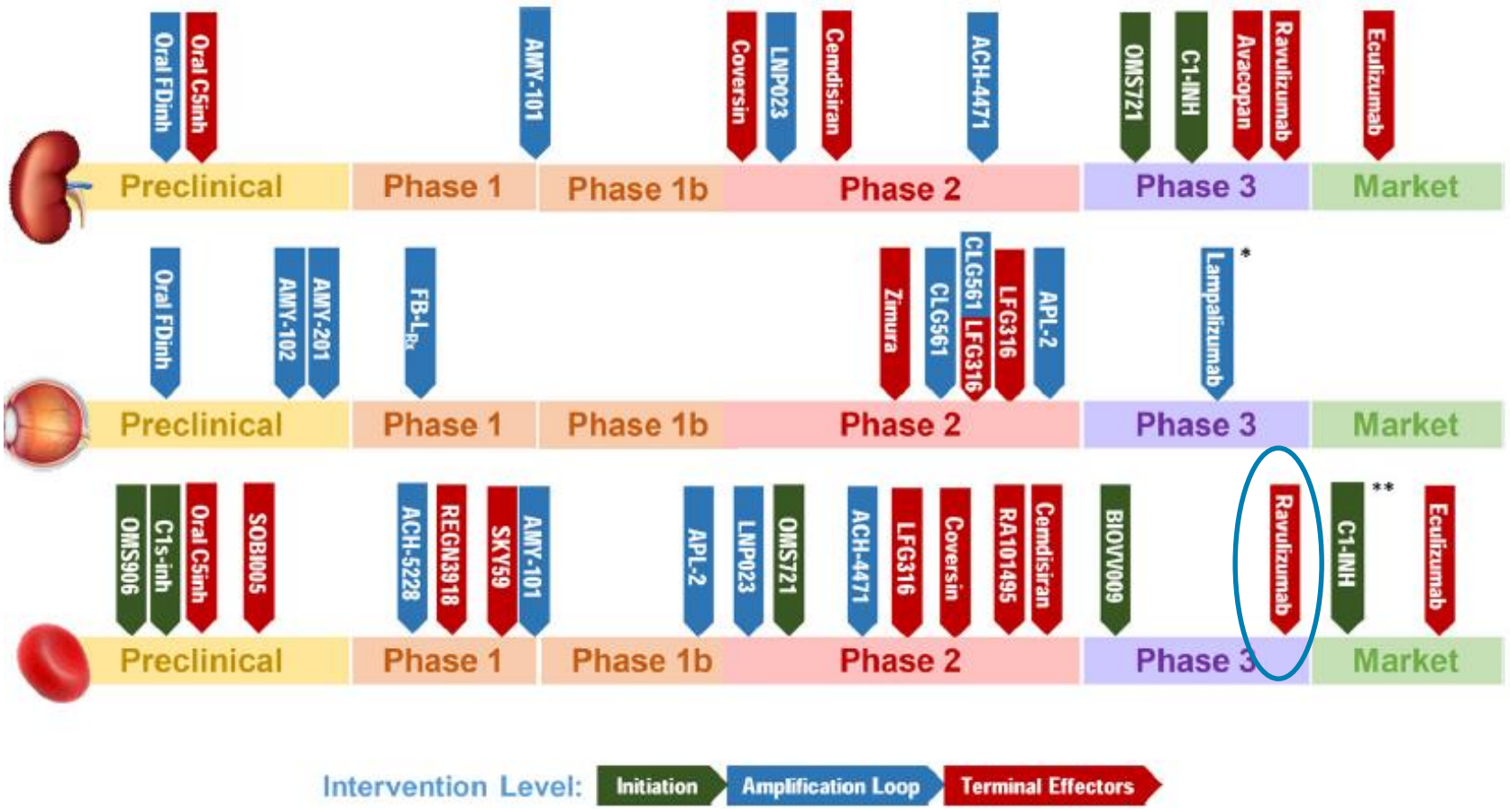


AD, Alzheimer's disease
AMD,Age-related macular degeneration
DAMP, damage-associated molecular pattern;
DDD, dense deposit disease;
PAMP, pathogen-associated molecular pattern;
PMN, polymorphonuclear cell;
PNH, paroxysmal nocturnal hemoglobinuria;
SLE, systemic lupus erythematosus.

Ricklin &Lambris J Immunol. 2013

Pipeline for anti-complement drugs in the kidney, eye and vasculature

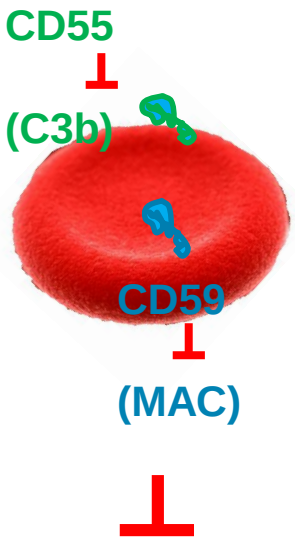
Harris et al., Molecular Immunology 102 (2018) 89–119



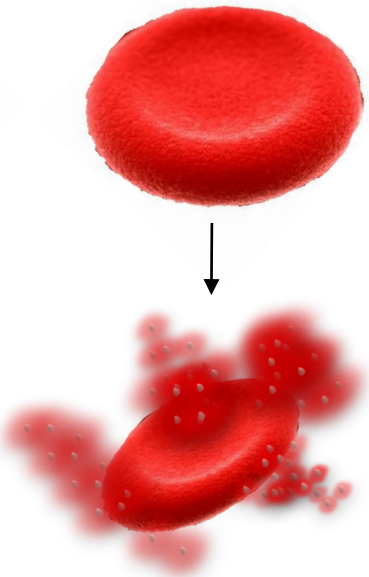
Half-life of ravulizumab is 4 times longer than that of eculizumab
(Lee et al., Blood, 2016)

Complement inhibition and hemolysis in PNH

No Complement activation

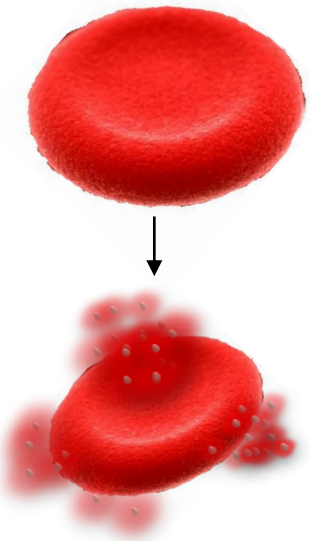


Complement Activation on PNH RBC



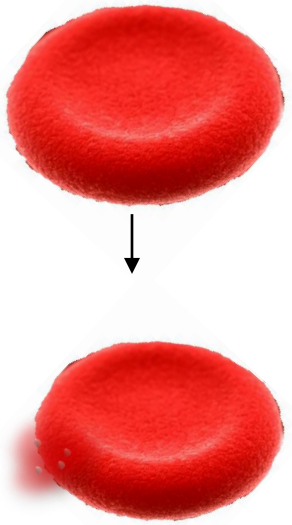
Lysis of PNH RBC
- Insertion of C5b-9 MAC (intravascular hemolysis)
- Opsonization with C3b (extravascular hemolysis)

Eculizumab
Complement Inhibition (C5 inhibition) on PNH RBC



Lysis of PNH RBC is still occurring
Opsonization with C3b (extravascular hemolysis)

Compstatin
Complement Inhibition (inhibition of C3b deposition) on PNH RBC→ impact on both pathways



Risk groups for IMD

Medical reasons

- Close contacts of patients with IMD;
  - **Subjects with a terminal complement deficiency or who are receiving anti-C5 treatment (and other future anti-complement treatment)**
  - **Subjects with other complement deficiencies (properdin Factor D)**
  - Subjects with anatomical or functional asplenia;
  - Subjects who received a hematopoietic stem cell transplantation
  - HIV
  - Association with viral infection (flu)

Occupational/societal reasons

Travellers, pilgrims, mass gathering events, military, laboratory staff working on meningococci, MSM, Students

Epidemic Situations

Complement and IMD

Inherited and drug induced complement deficiencies.

- 13% of IMD revealed complement deficiencies in South Africa (Owen *et al.*, *S Afr Med* 2012).
- One third of group Y IMD revealed complement deficiency France (Le Bastard et al., Pathol Biol, 1989).
- 7/22 (32%) patients with NG IMD had complement deficiency or abnormal complement testing results (McNamara *et al.*,, *Open Forum Infect Dis* 6, 2019).
- Among 160 patients with complete TPD; 56 patients (39%) showed confirmed IMD (France 1999-2015)(Rosain et al., J.Infect Dis 2017)
- 16 patients in England with inherited or acquired complement deficiencies (2008-2017) (Ladhani et al., BMC Infect Dis 2019).

Complement deficiencies and IMD: Isolates

Rosain et al., J.Infect Dis 2017, El Sissy *et al.*, *Frontiers in Immunology* 2019) **: France 1999-2018**

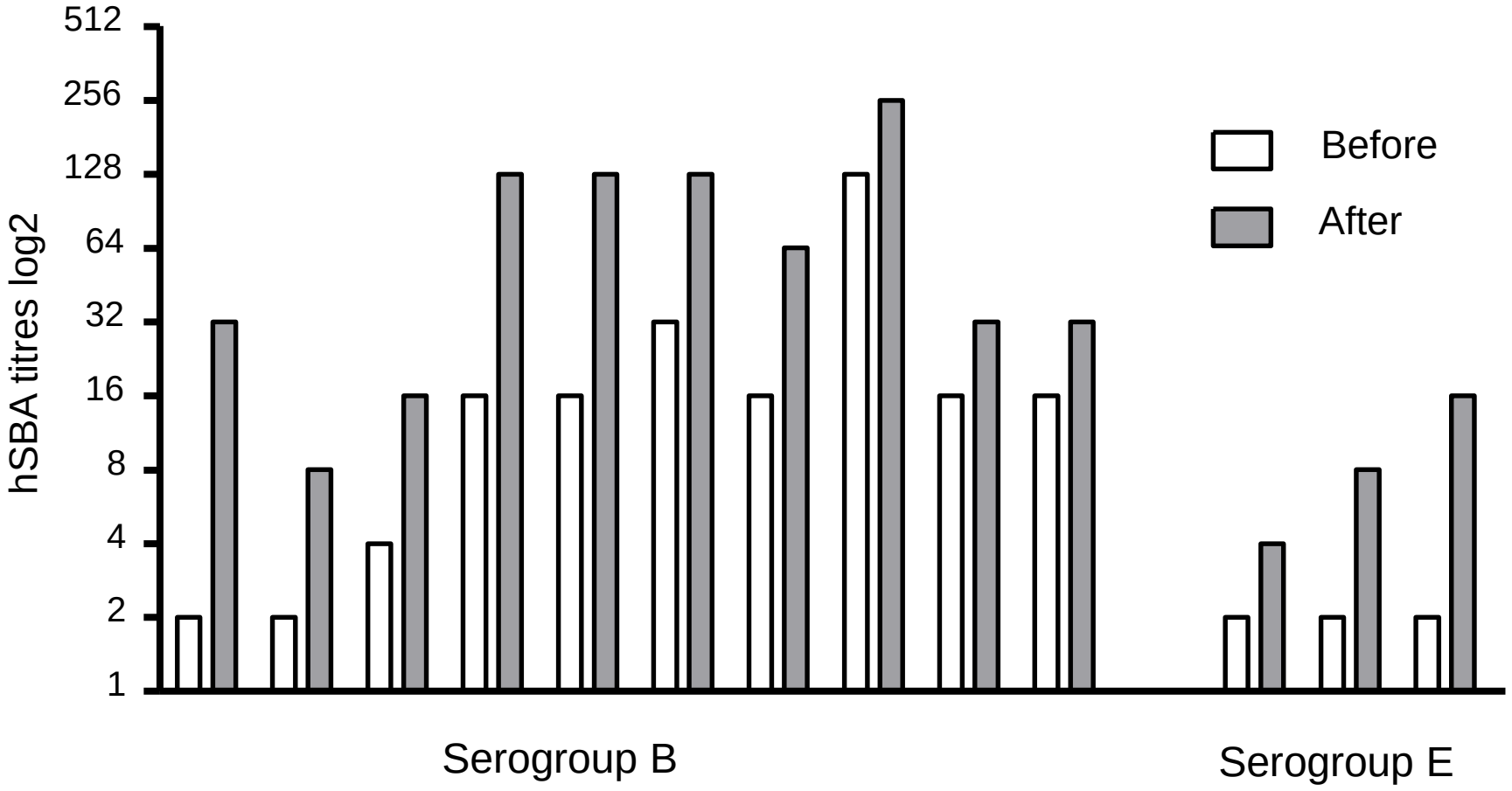
Type of deficiency	N° of isolates/episodes (patients)	Isolates (n)	Fatal cases
TPD	63 (59)	B(19); C(2); Y(29); W(9); E(4); NG(1)	1
Factor D	1 (1)	B (1)	0
Properdin	1 (1)	Y (1)	1
Eculizumab	3 (3)	Y(2); C(1)	0

Ladhani et al., BMC Infect Dis 2019 : **England 2008-2017**

Type of deficiency	N° of isolates/episodes (patients)	isolates
Inherited	11(8)	B(3); Y(7); NG(1)
Eculizumab	9 (8)	B(3+3NG); Y(1); W(1); E(1)

- Heterogeneous isolates
- Frequent Y, E and NG isolates
- Only 21% belonging hyper-invasive CC (France)

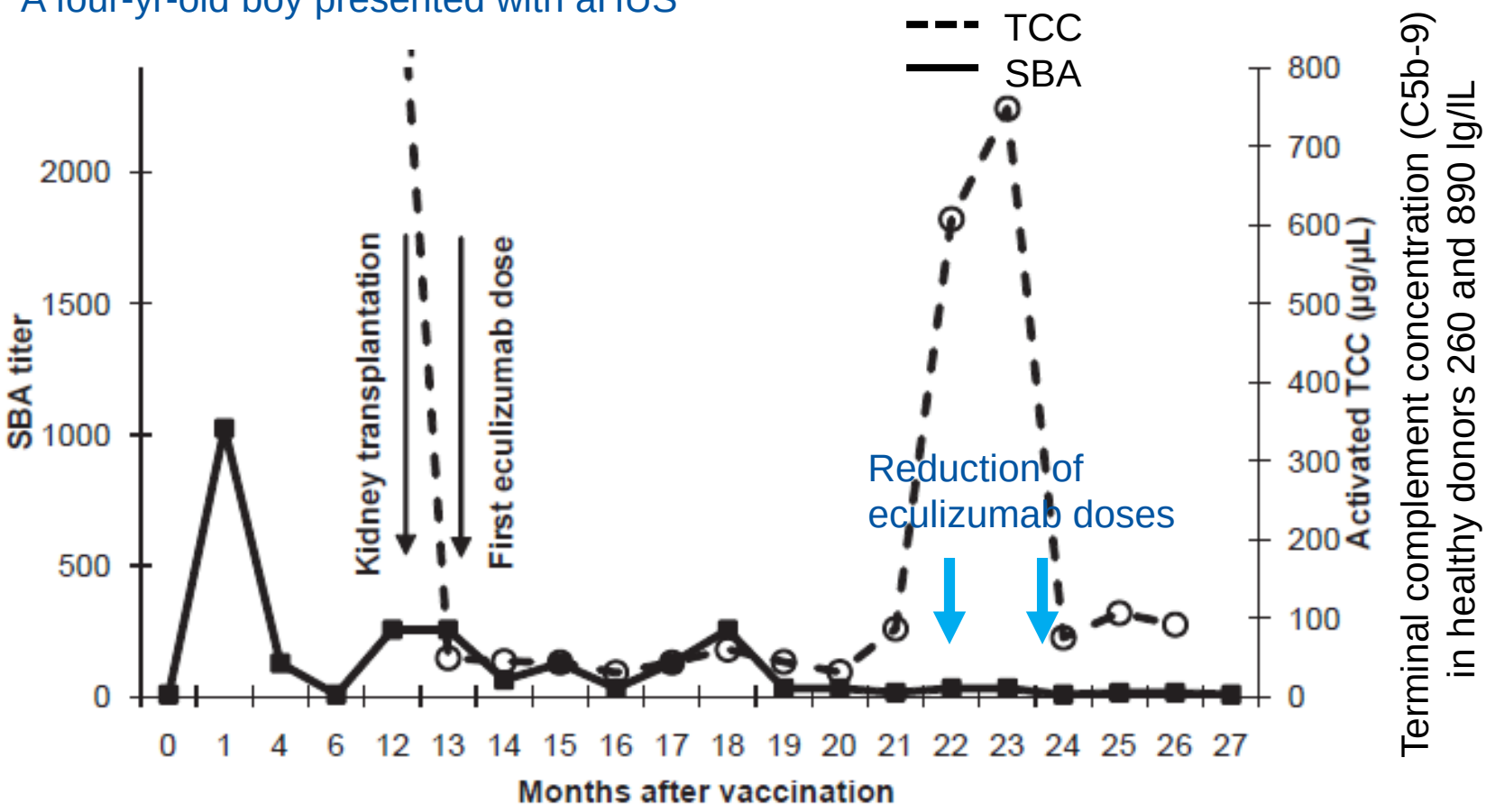
Coverage of serogroup B and E isolates of the TPD patients by the 4CMenB vaccine



Data NRC, Institut pasteur

Immunogenicity of MCC in a patient with aHUS on eculizumab therapy

A four-yr-old boy presented with aHUS



- TCC concentration reflects the ability to activate the complement system
- But SBA response seems to be impaired under treatment

Zlamy et al., Pediatr Transplantation 2012:

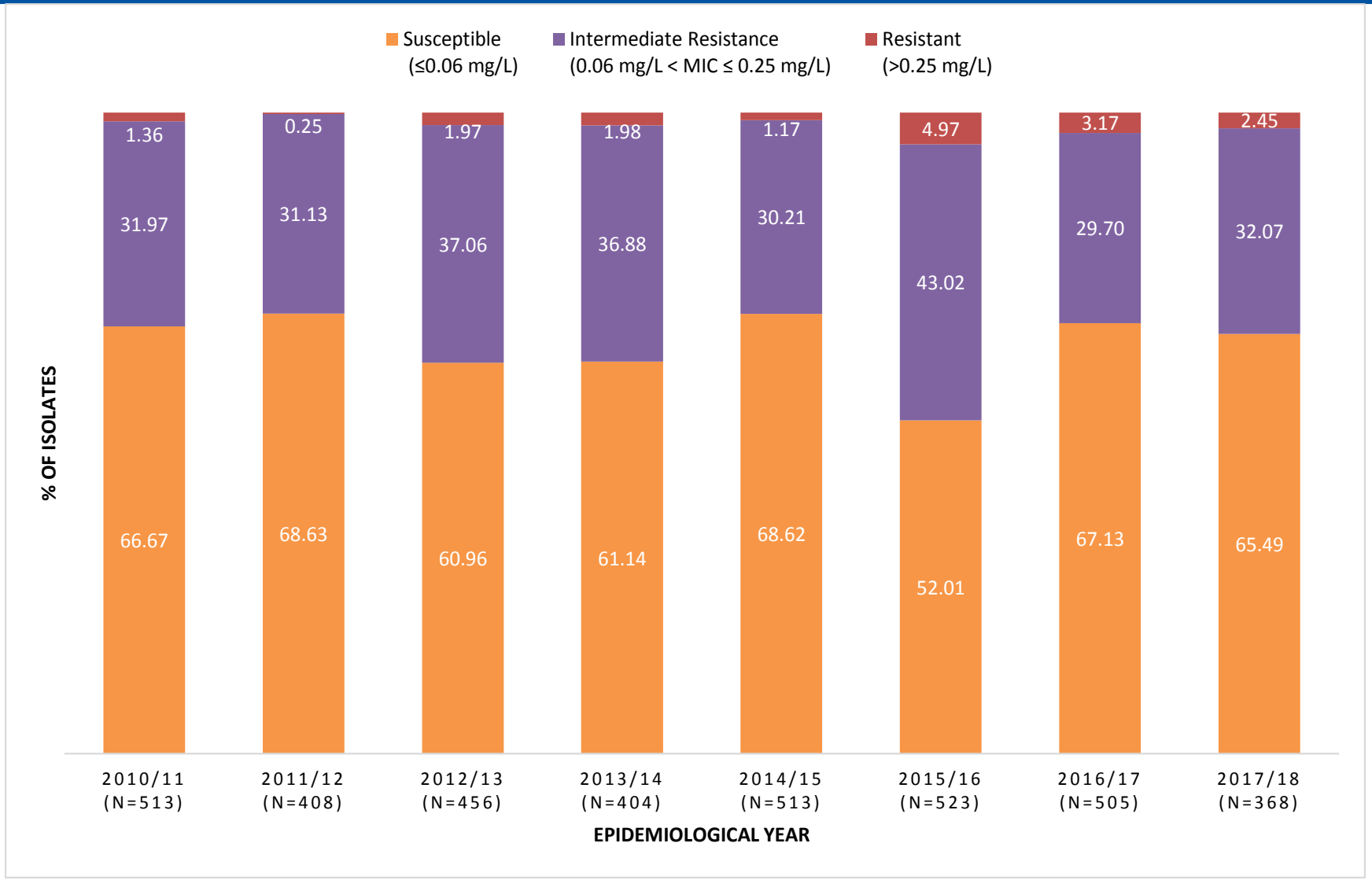
Penicillin-resistant case of IMD in patient on Eculizumab therapy

- Case of IMD due to a vaccine-preventable and penicillin-resistant strain in a fully immunised young adult (22 years) on long-term complement inhibitor therapy and daily penicillin chemoprophylaxis.
- First case of meningococcal group B vaccine failure in a young adult receiving Eculizumab for aHUS.
- Developed IMD due to capsular group B 4 months after receiving 2 doses of 4CMenB vaccine while on oral penicillin prophylaxis.
- Strain ST-162 (pathogenic potential).
- Capsular gene SiaDb interrupted by an insertion sequence.
- PenA allele contained 3 mutations associated with reduced penicillin sensitivity.
- PenA allele previously associated with *N. gonorrhoeae.*
- Strain confirmed covered by 4CMenB by MATS by NHBA antigen.

Courtesy from Prof R. Borrow

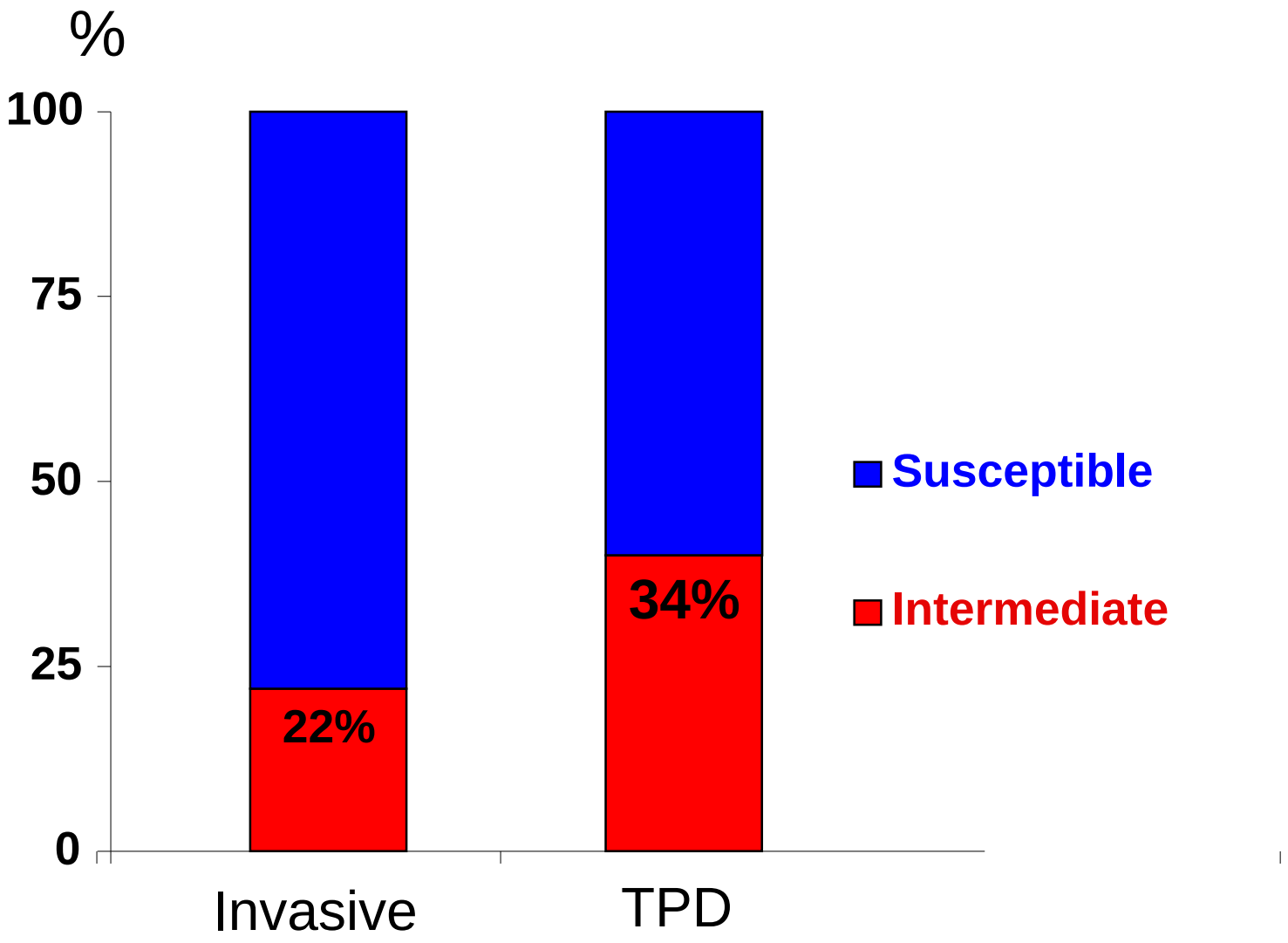
Parikh SR et al. Pediatrics. 2017 Sep;140(3). pii: e20162452.

Penicillin resistant in England, Wales and Northern Ireland (2010/11-2017/18)



Courtesy from Prof R. Borrow. PHE unpublished data.

Susceptibility to penicillin G

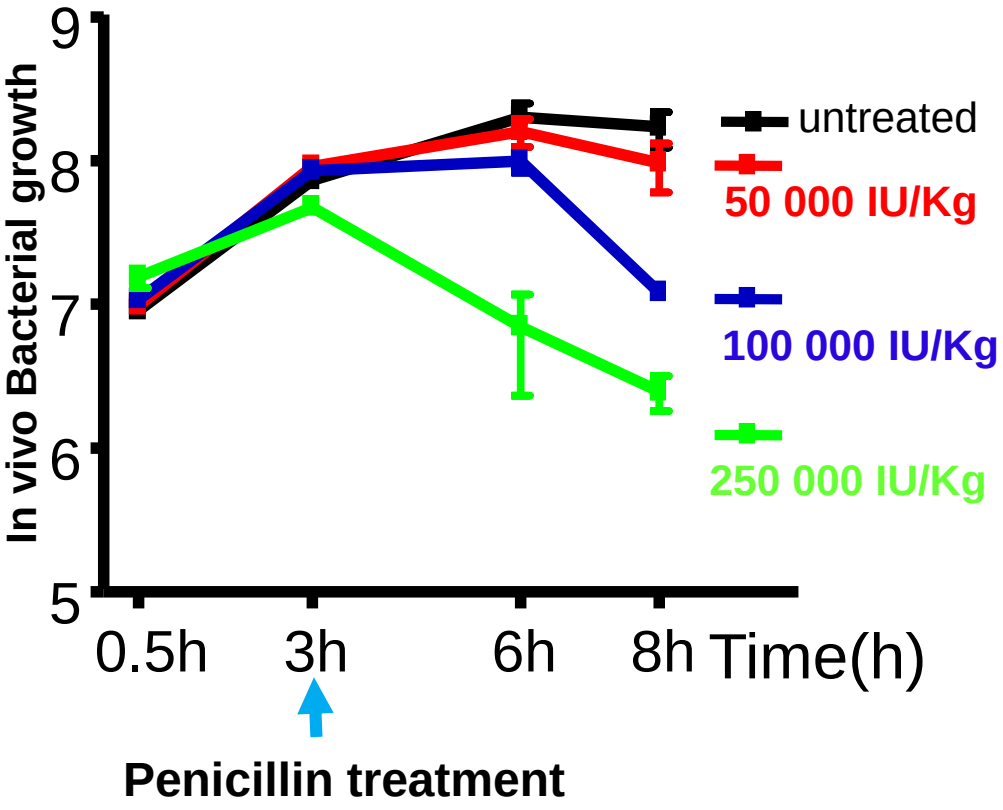


Data NRC, MK Taha, Institut pasteur, Unpublished data

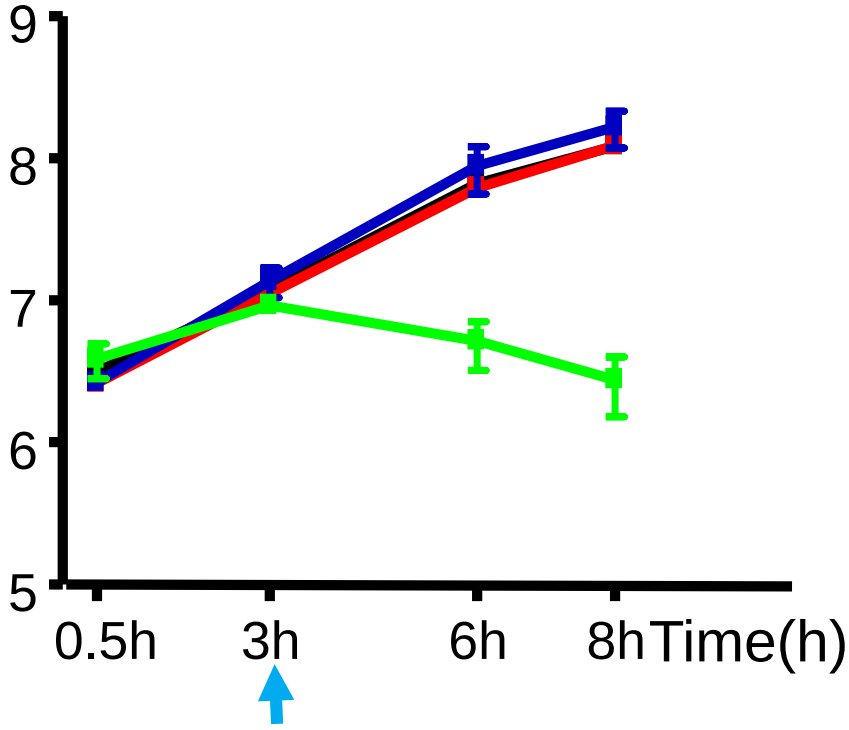
Penicillin is still effective against intermediate (resistant) isolates (mouse model)

Mice infected i.p. with isogenic susceptible or intermediate isolates (MIC0.5mg/L)

Susceptible isolate (MIC <0.064 mg/L)



Intermediate (resistant) isolate (MIC 0.5 mg/L)



Belkacem *et al.*, *Antimicrob Agents Chemother* 2016).

Conclusions (1)

- Increasing evidence of association of complement activation and degenerative diseases
- Anti-complement treatment may be benefic
- Complement deficiencies can be associated with increase susceptibility to IMD.
- Serogroup Y isolates predominate but NG can be important under anti-complement treatment

- Explore complement systematically when IMD is provoked with non hyperinvasive isolates.
- Explore complement systematically if IMD with vaccine preventable serogroup in vaccinated patients.
- If an inherited complement deficiency confirmed in the patient then explore the members of the family.
- Exploration of not only the determination of the CH50 activity but also the alternative pathway.

Conclusions (2)

- Vaccination of subjects with complement deficiencies (inherited and acquired) against ACWY and B
- Vaccination in not enough. Antibiotic treatment is required (High dose penicillin V ≥ 250 000 IU/Kg/day).
- Rescue antibiotics (i.e. self-treatment with a treatment course of amoxicillin (+ penicillin), ciprofloxacin or other antibiotics to be defined when unwell)?
- Vaccination of household contacts of subjects with complement deficiencies (cocooning strategy).