



UNIVERSITA' DEGLI STUDI DI MESSINA
A.O.U. POLICLINICO G. MARTINO - DIPARTIMENTO MATERNO
INFANTILE

U.O.C. Pediatria d'Urgenza con P.S. e O.B.

Centro Riferimento Regionale Prevenzione, Diagnosi e Cura delle Malattie Genetiche
Centro IPINET (Italian Primary Immunodeficiency Network)

Direttore: Prof. Carmelo Salpietro



INFEZIONI DA MENINGOCOCCO

Con il patrocinio di :

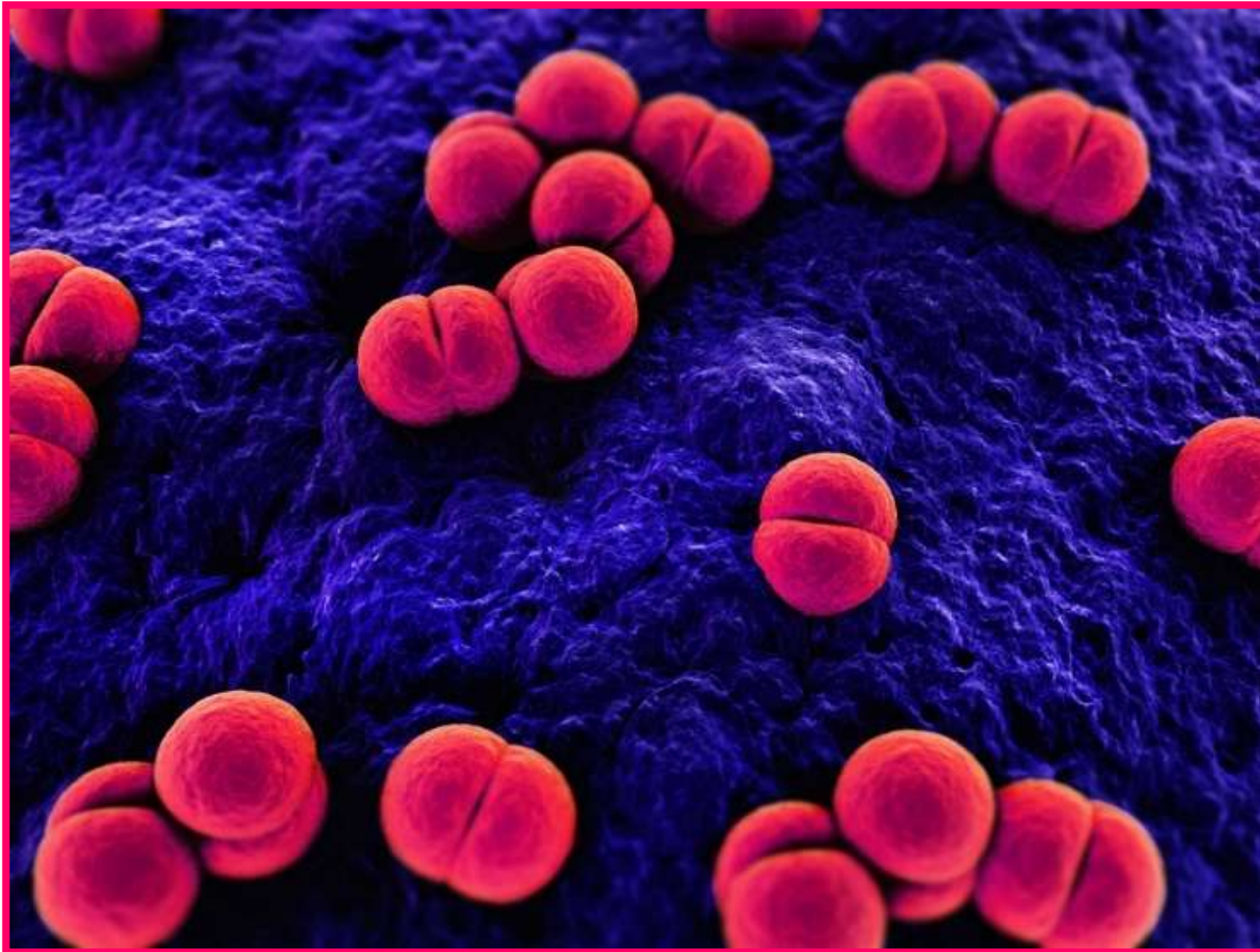


COMUNE DI COMISO



**Carmelo
Salpietro**

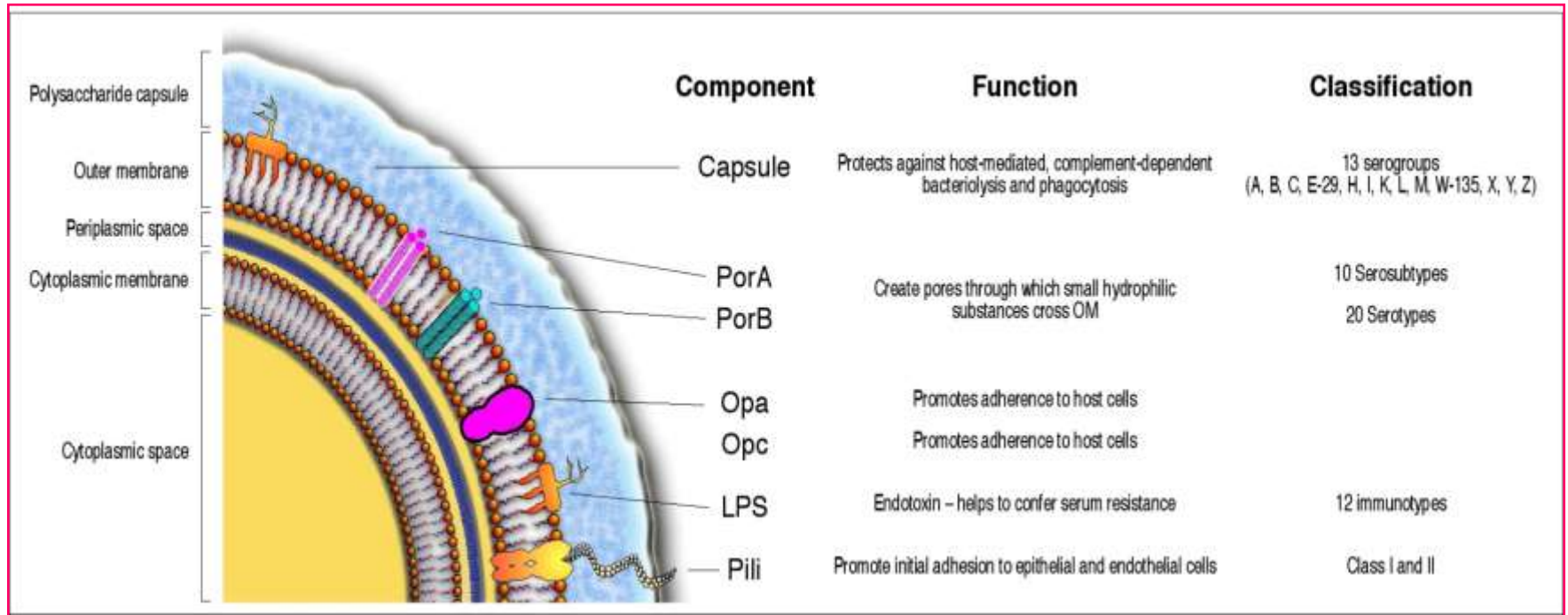
NEISSERIA MENINGITIDIS



- Diplococco Gram negativo
- Capsulato o non

- Aerobico
- Ossidasi-positivo

NEISSERIA MENINGITIDIS

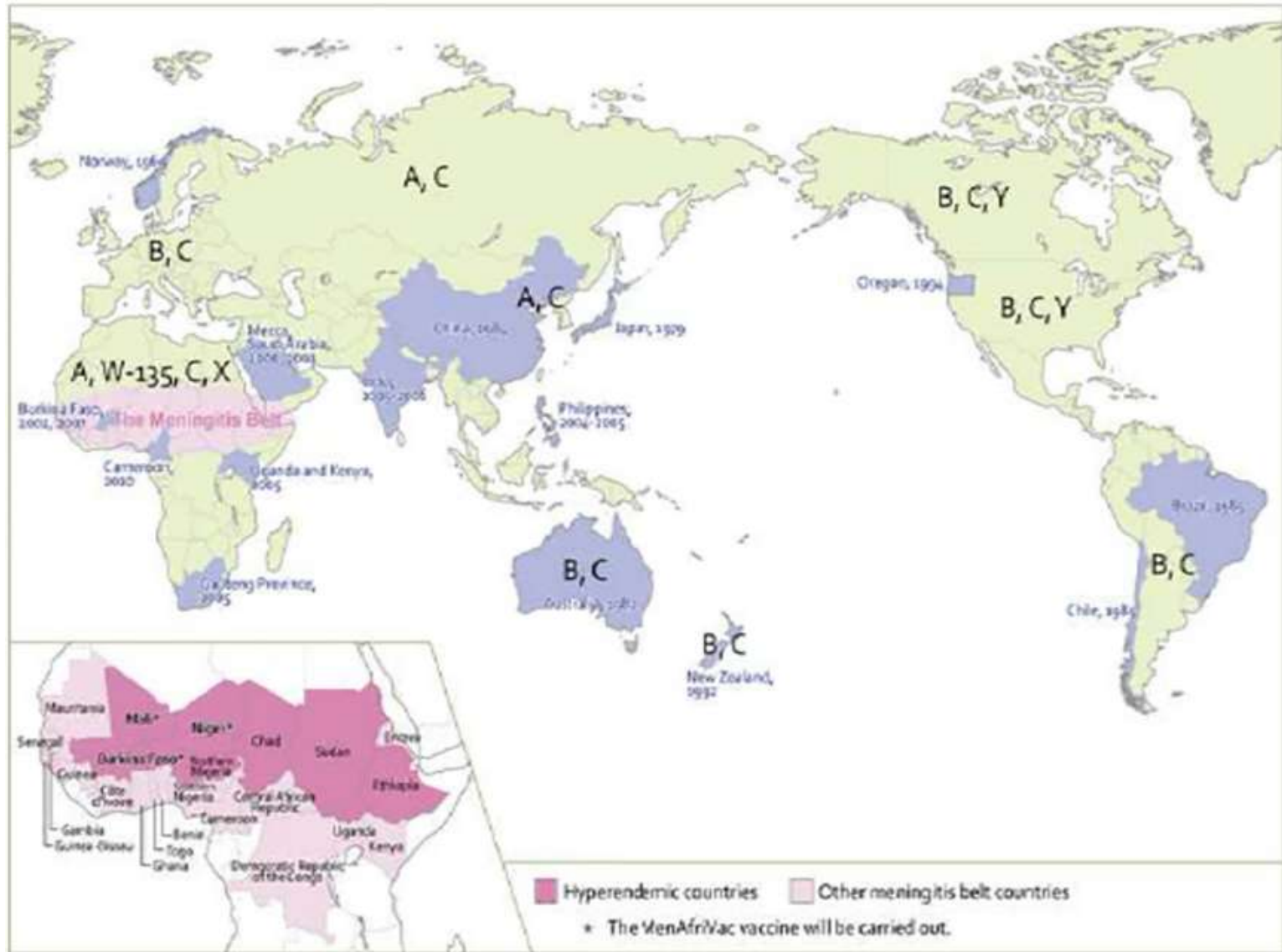


13 SIEROGRUPPI (A, B, C, D, 29E, H, I, K, L, W-135, X, Y, Z)
sulla base alla diversità antigenica dei polisaccaridi capsulari



95% dei casi di malattia invasiva sono causati da 5 sierogruppi

DISTRIBUZIONE NEL MONDO DEI MAGGIORI SIEROGRUPPI



beatrice morta per uno shock settico

L'addio alla ragazza in un silenzio inecchabile

di Francesco...
 di Francesco...
 di Francesco...



IL CASO DI MESTRE

Stazionario il giovane colpito da meningite

«Non c'è aggravamento e in tutte le malattie batteriche è un...
 «Non c'è aggravamento e in tutte le malattie batteriche è un...
 «Non c'è aggravamento e in tutte le malattie batteriche è un...»

Lacrime per Laura: è morte cerebrale

Uccisa dalla meningite la ragazzina tedesca di 16 anni in gita scolastica nelle 5 Terre



«Non c'è aggravamento e in tutte le malattie batteriche è un...»
 «Non c'è aggravamento e in tutte le malattie batteriche è un...»
 «Non c'è aggravamento e in tutte le malattie batteriche è un...»

In coda per il vaccino e c'è chi...

Stazionarie le condizioni del diciassettenne di Zelarino in coma



«Non c'è aggravamento e in tutte le malattie batteriche è un...»
 «Non c'è aggravamento e in tutte le malattie batteriche è un...»
 «Non c'è aggravamento e in tutte le malattie batteriche è un...»

Il caso

Allarme meningite a Roma, muore una maestra

L'insegnante deceduta lunedì, era rimasta al lavoro fino al 22 dicembre. Decine di alunni sottoposti a profilassi



«Non c'è aggravamento e in tutte le malattie batteriche è un...»
 «Non c'è aggravamento e in tutte le malattie batteriche è un...»
 «Non c'è aggravamento e in tutte le malattie batteriche è un...»

Meningite, assedio a medici e ospedale

Centinaia di giovani in fila in gita e al telefono

L'ALLARME SANITARIO

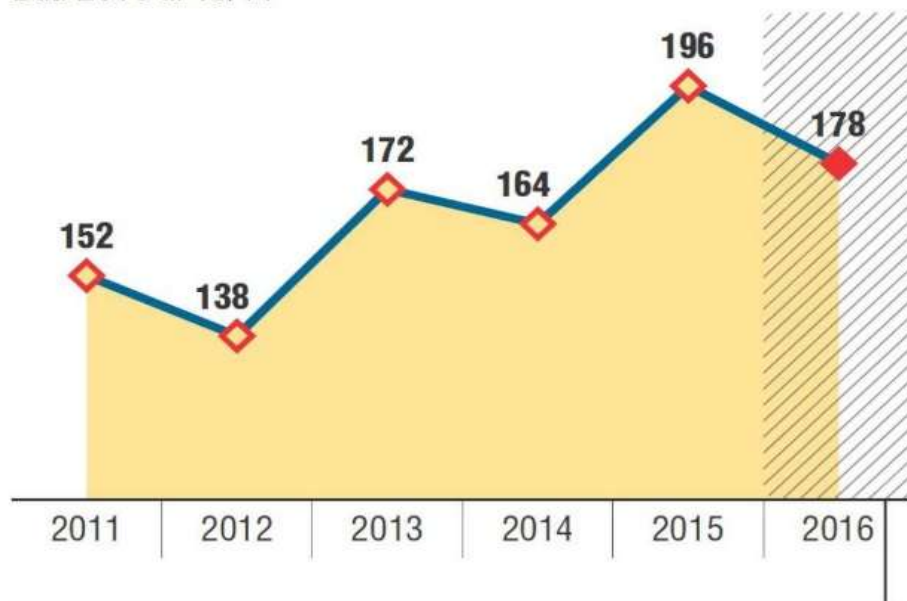
La ventottenne è stata trascina...
 di vaccinazione gratuita per il vaccino B"



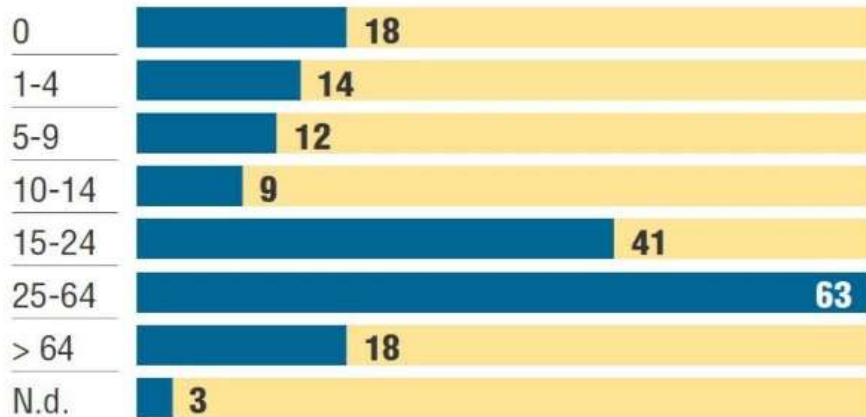
La meningite in Italia

Casi da meningococco (la forma più contagiosa e pericolosa) negli ultimi anni

Dati 2016 al 16/11



PER CLASSE DI ETÀ (anni)



PER REGIONE



Increased incidence of invasive meningococcal disease of serogroup C / clonal complex 11, Tuscany, Italy, 2015 to 2016

P Stefanelli¹, A Miglietta², P Pezzotti¹, C Fazio¹, A Neri¹, P Vacca¹, F Voller³, FP D'Ancona^{4,5}, R Guerra⁵, S Iannazzo⁵, MG Pompa⁵, G Rezza¹

FIGURE 1

Annual distribution of serogroup C invasive meningococcal disease cases by outcome, January 2000-February 2016 (n=111 cases) (A) and monthly distribution, January 2015- February 2016 (n=43 cases), Tuscany, Italy

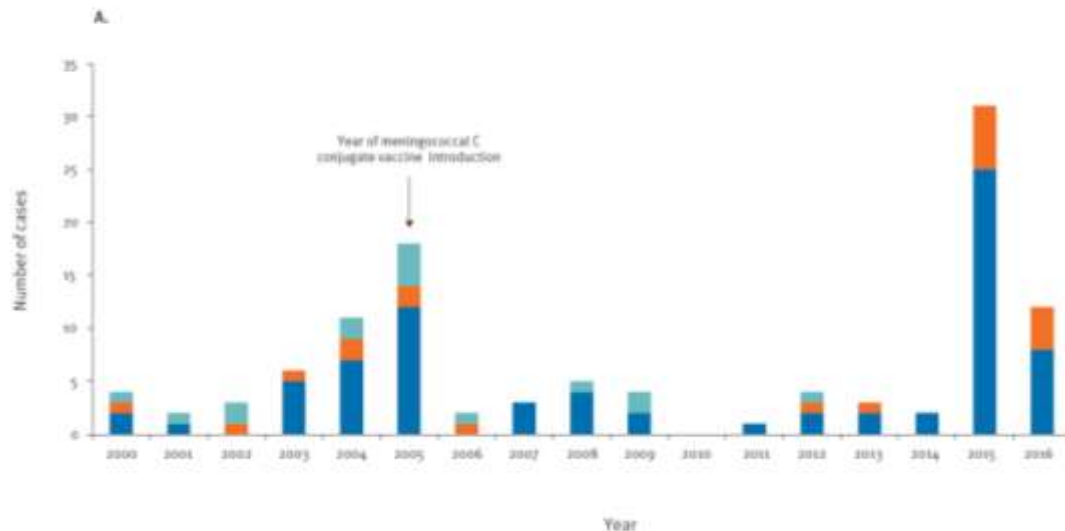


FIGURE 2

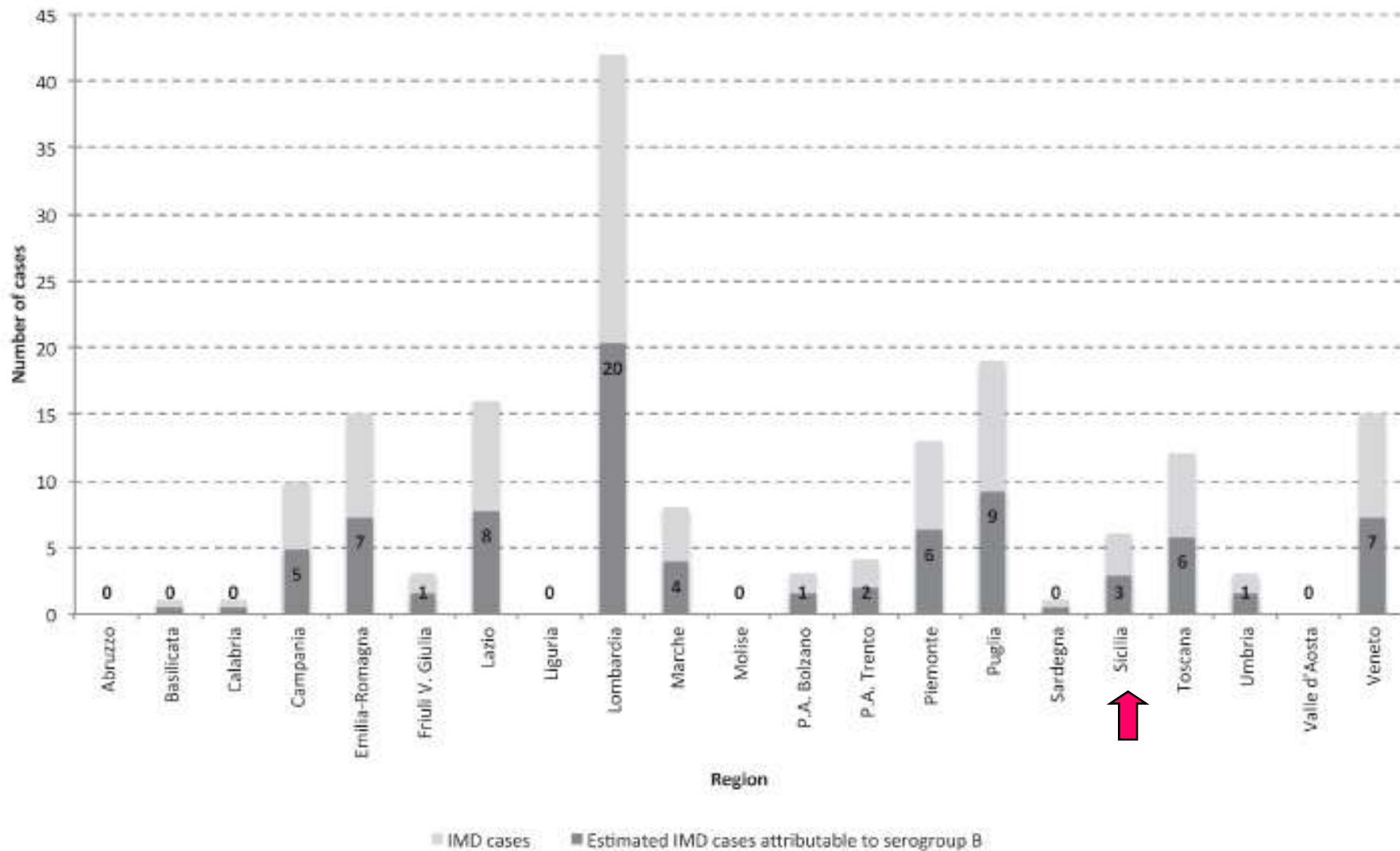
Number (A) and incidence rate per 100,000 inhabitants (B) of serogroup C invasive meningococcal disease by municipality of symptom onset, Tuscany, Italy, January 2015 to February 2016



■ Cases ■ Fatal cases ■ No information available

Estimates of the burden of meningococcal disease in Italy: implications for prevention and control

D. MARTINELLI, F. FORTUNATO-R. PRATO
Department of Medical and Surgical Sciences, University of Foggia



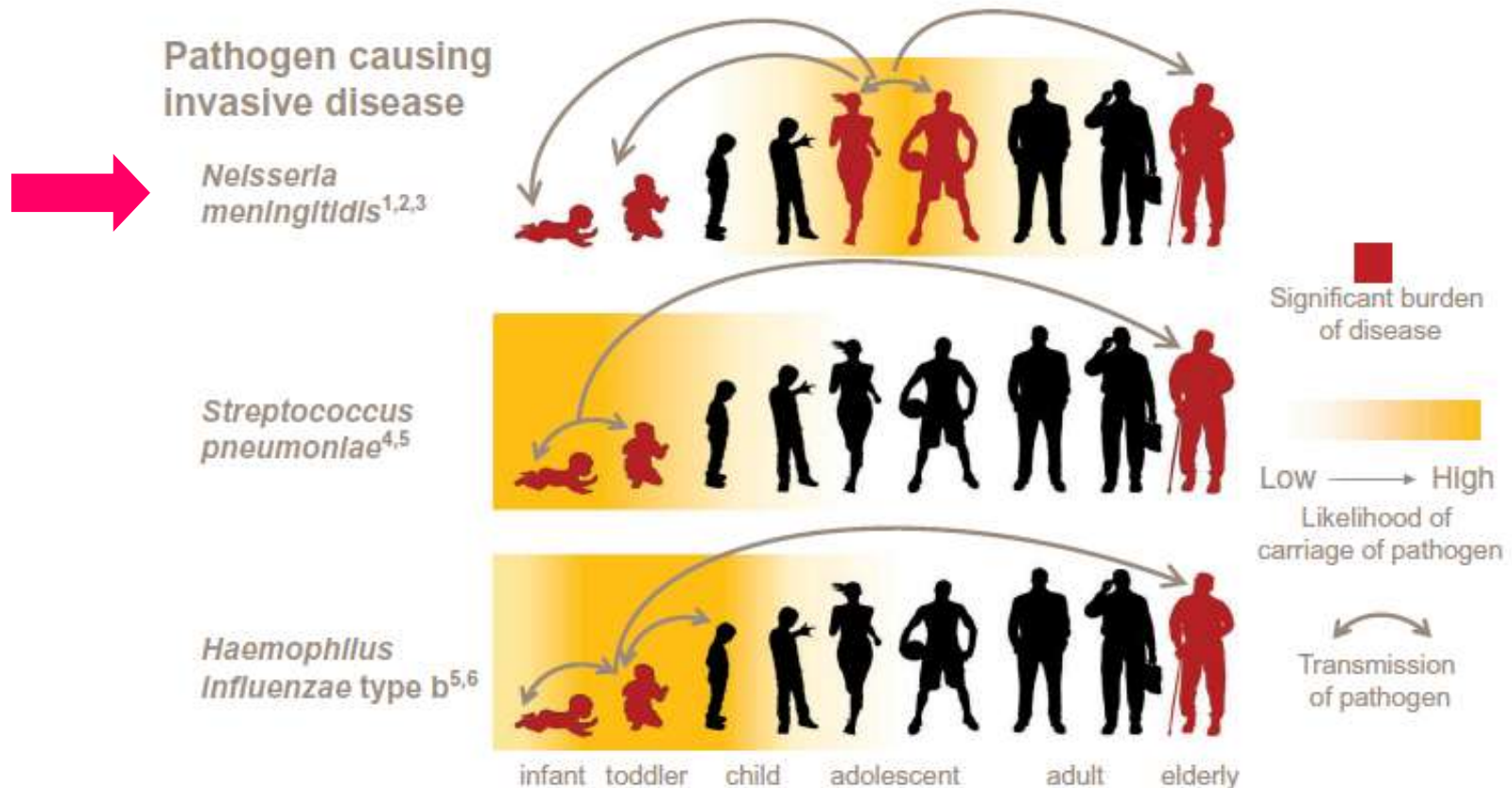
Number of invasive meningococcal disease cases and estimated distribution of cases attributable to **serogroup B**, by Italian region, 2013

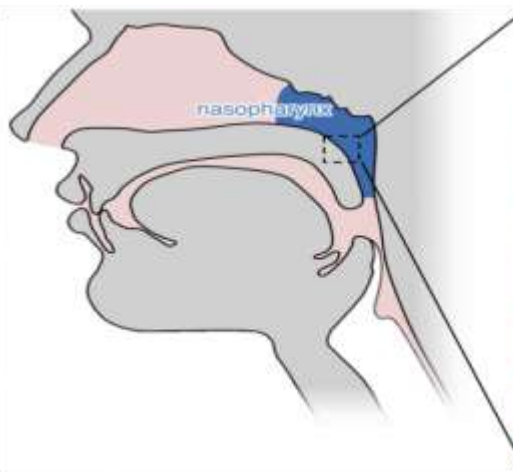
REVIEW

 OPEN ACCESS

Routinely vaccinating adolescents against meningococcus: targeting transmission & disease

Volker Vetter^a, Roger Baxter^b, Gülhan Denizer^a, Marco A. P. Sáfaci^c, Sven-Arne Silfverdal^d, Andrew Vyse^a and Ray Borrow^e



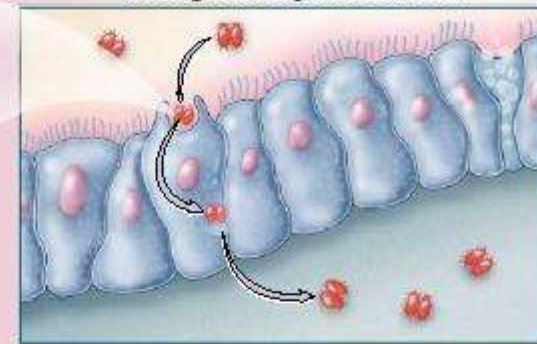


Nasopharyngeal mucosa

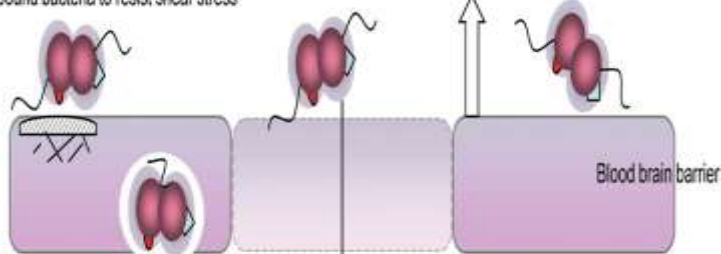


Attachment to and interaction with nasopharyngeal epithelium

Passage through the mucosa

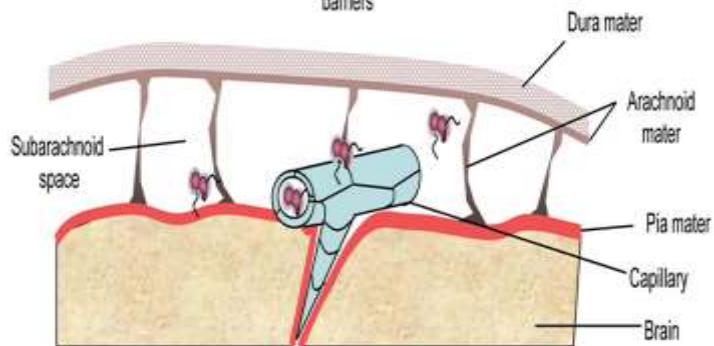


Lipid microdomain formation and cytoskeletal rearrangements may enable bound bacteria to resist shear stress



IL-6
IL-8
TNF- α

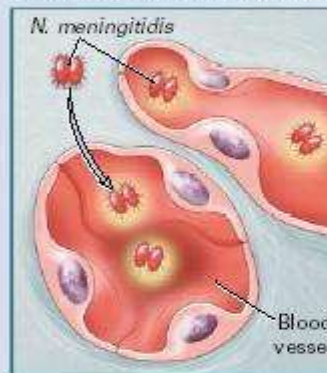
Cytokine damage may increase bacterial transcytosis of all cell barriers



Cytokine release following interaction of bacteria with the leptomeninges leads to meningitis

Blood

Survival in the bloodstream



Factors affecting intravascular survival

- Capsule: protects against complement-mediated bacteriolysis and phagocytosis
- Acquisition of iron from transferrin

Endotoxin and other cell components

Host-cell cytokine production

Alternative complement pathway

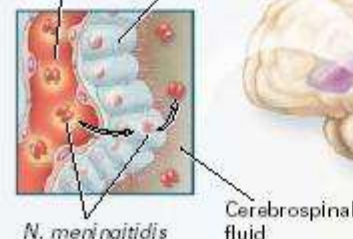
Inflammatory cytokines (tumor necrosis factor α , interleukin- β , 6, 8)

Antiinflammatory cytokines (interleukin-10)

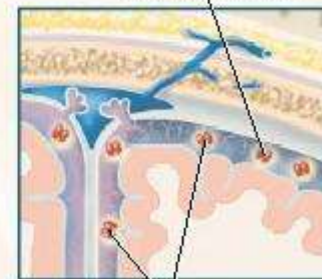
Cerebrospinal fluid

Crossing of the blood-brain barrier

Blood vessel Blood-brain barrier endothelium

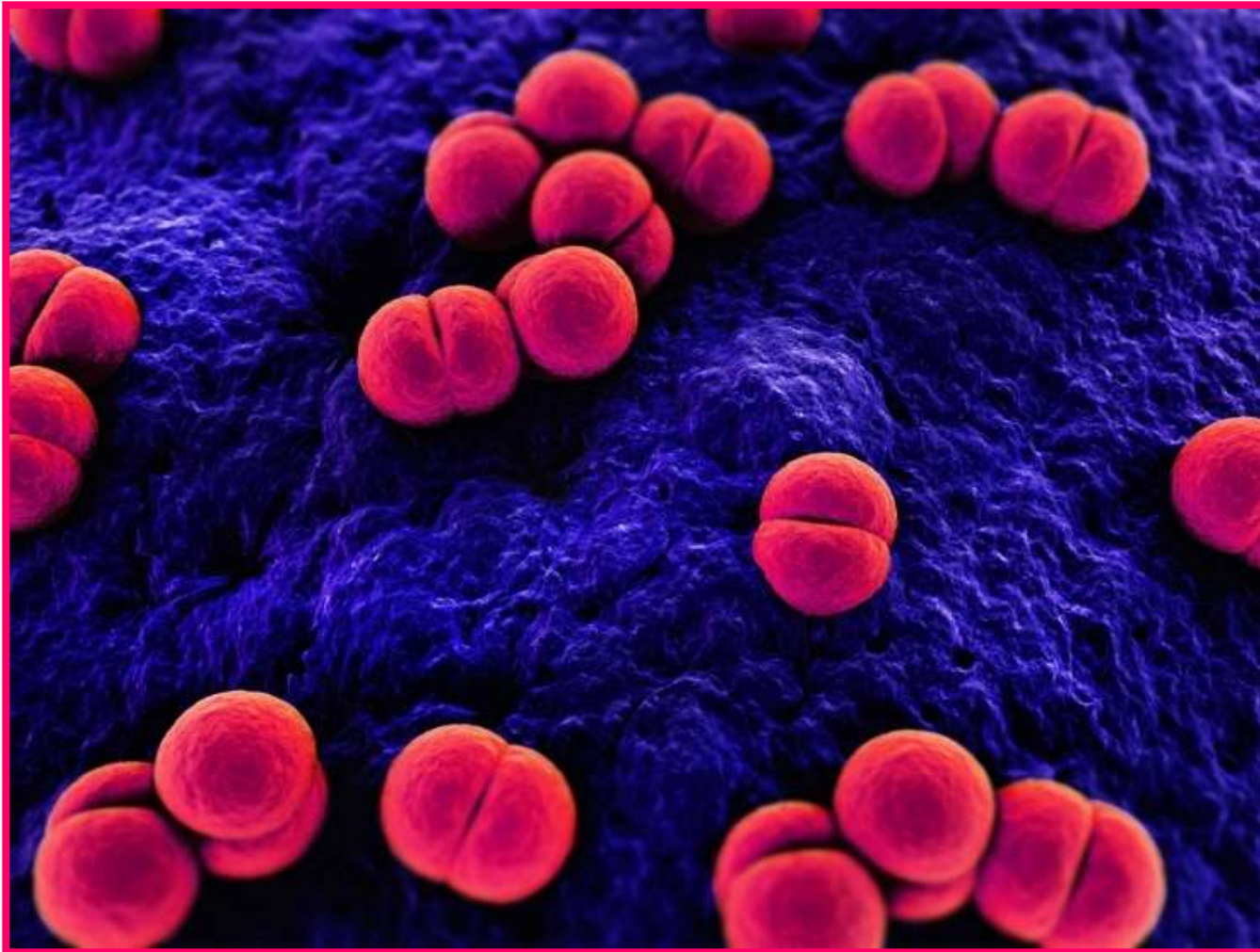


Multiplication in subarachnoid space



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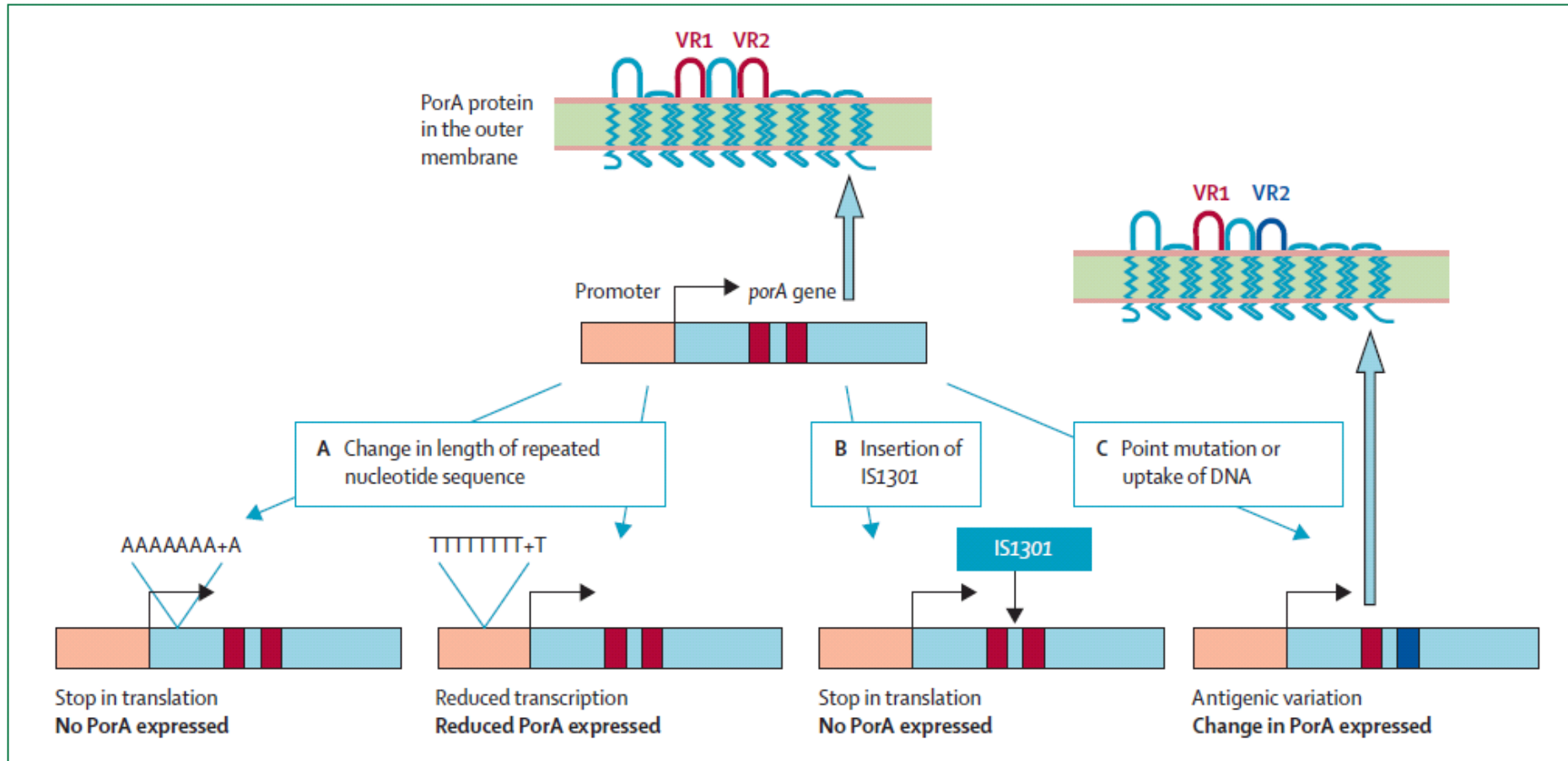
NEISSERIA MENINGITIDIS



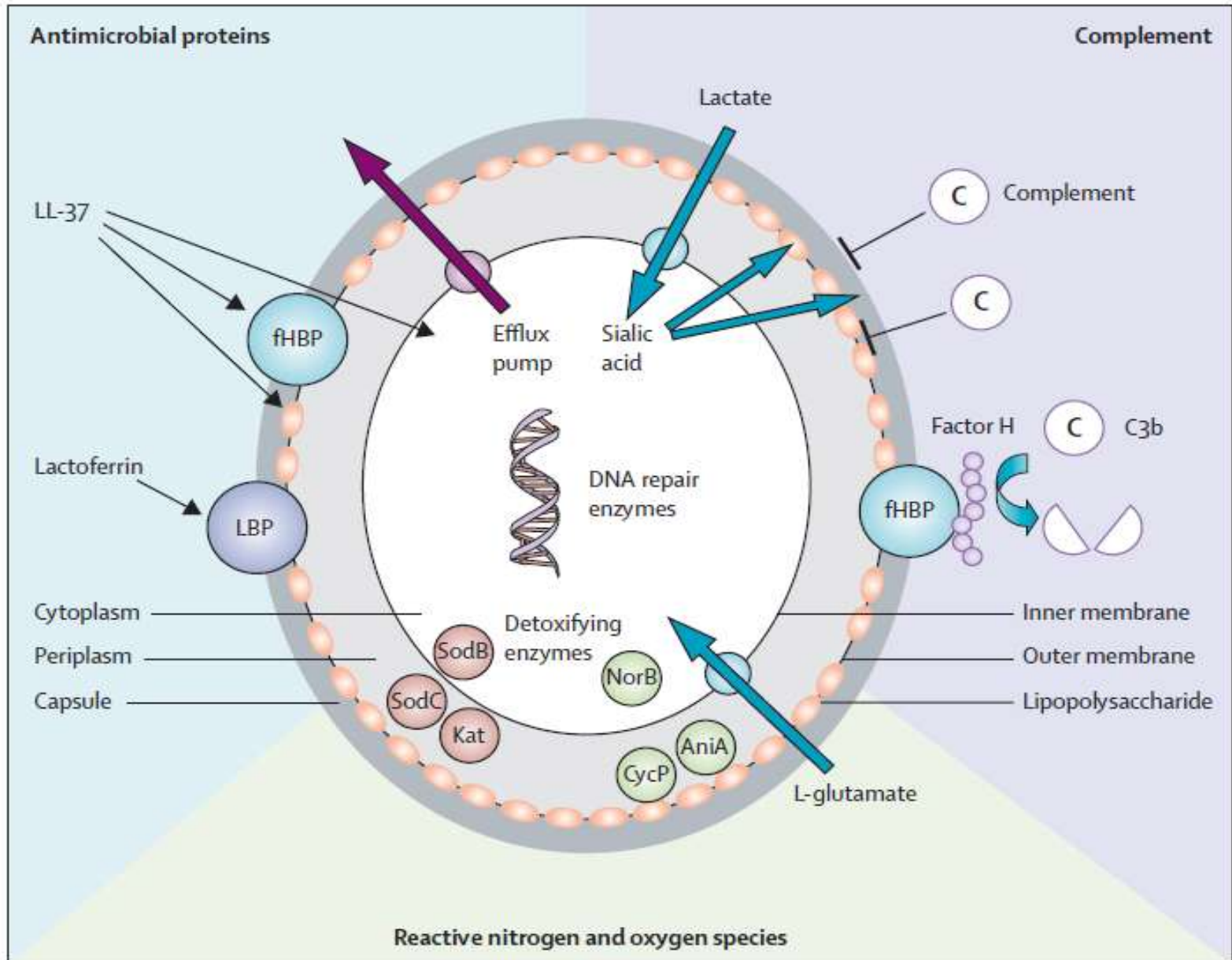
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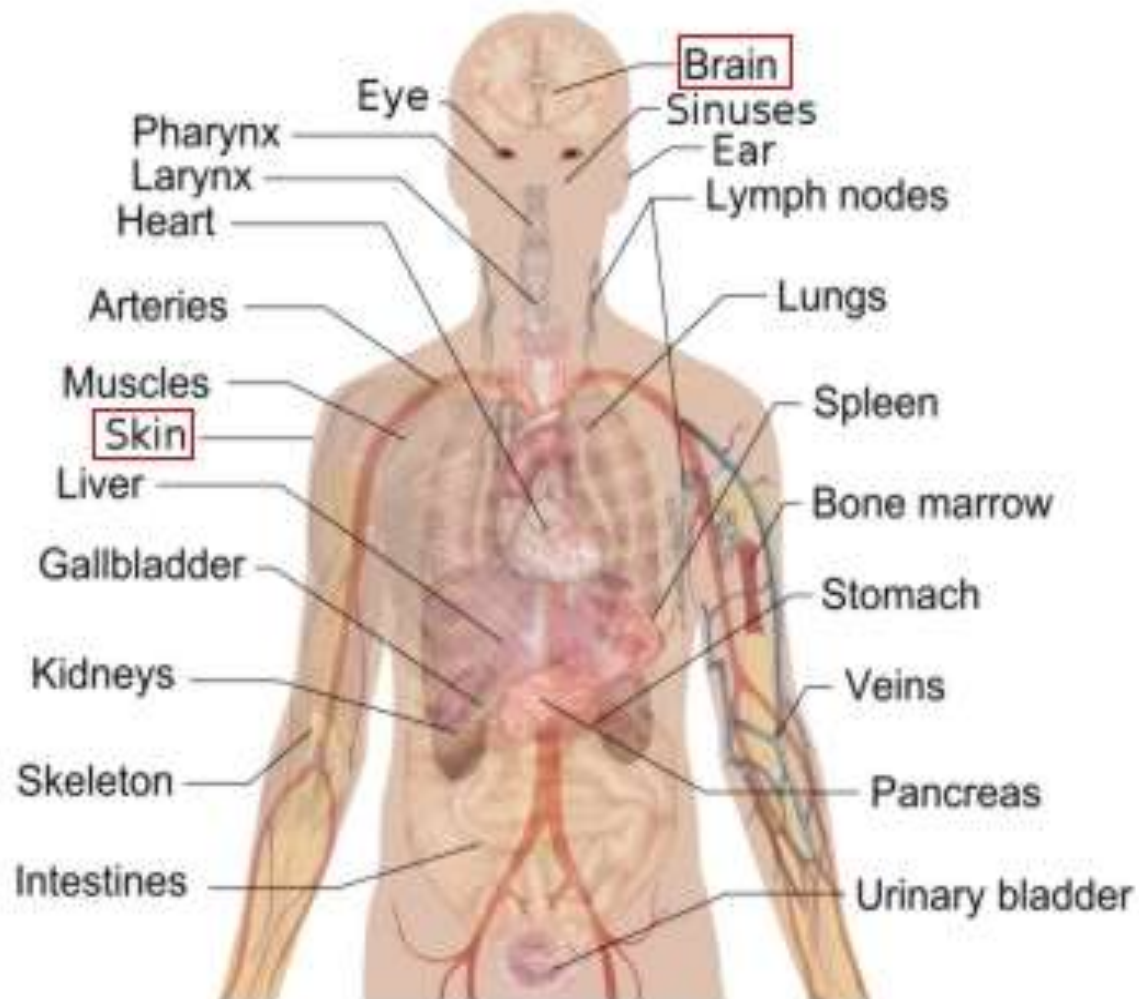
MENINGOCOCCO: DIVERSITÀ GENETICA DINAMICA DEL POR A X SUPERARE IL SISTEMA IMMUNITARIO DELL'OSPITE



I MECCANISMI CON CUI IL MENINGOCOCCO SOVERTE LE DIFESE DELL'OSPITE



Neisseria meningitidis INFECTIONS



POLIMORFISMI GENETICI ASSOCIATI CON INFENZIONE MENIGOCOCCICA

IMMUNITA' INNATA

IMMUNITA' ACQUISITA

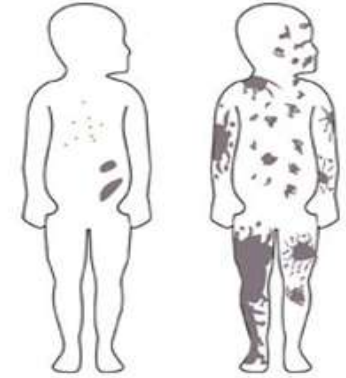
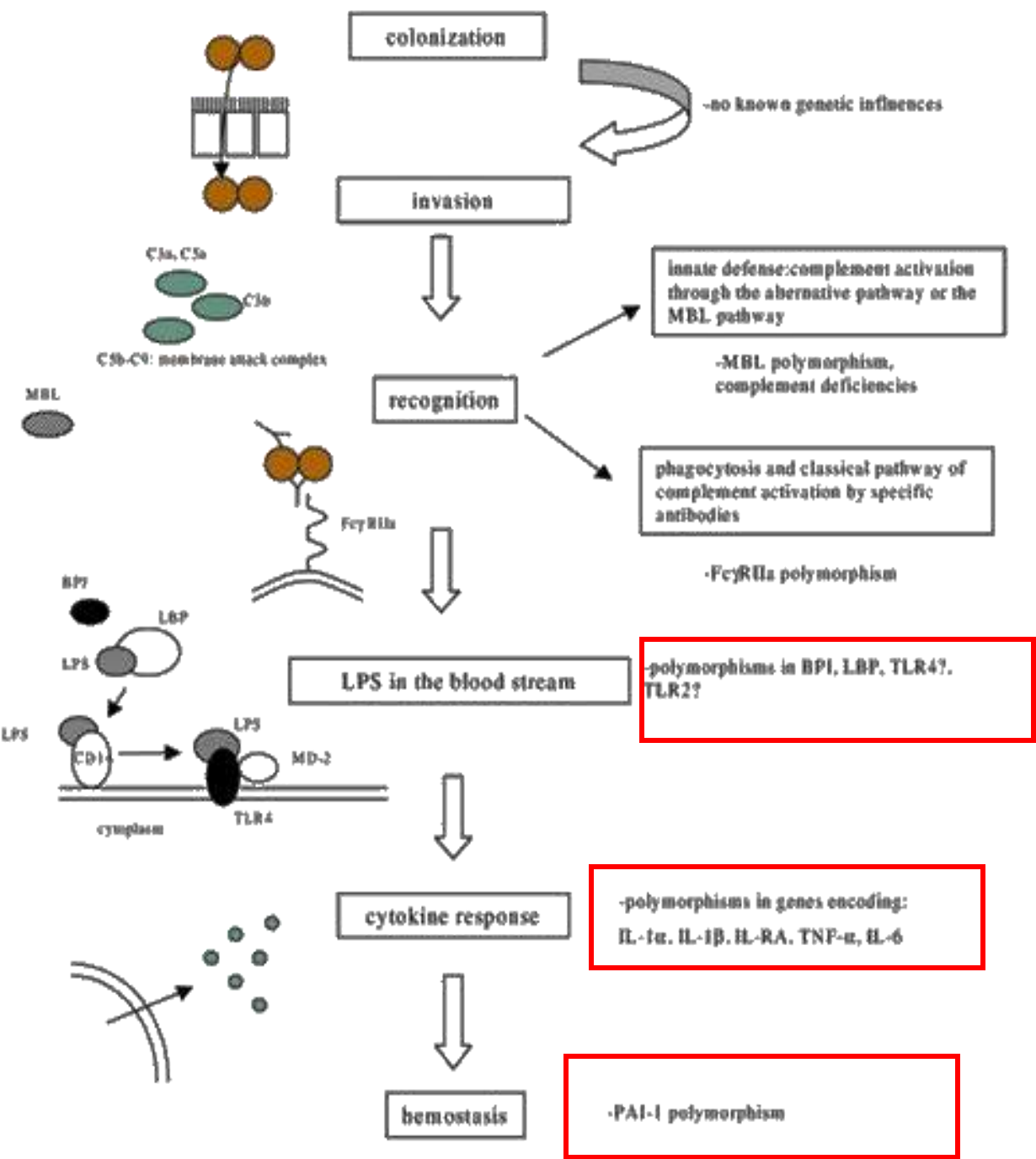
COAGULAZIONE

CITOCHINE

Genetic polymorphisms associated with meningococcal infection

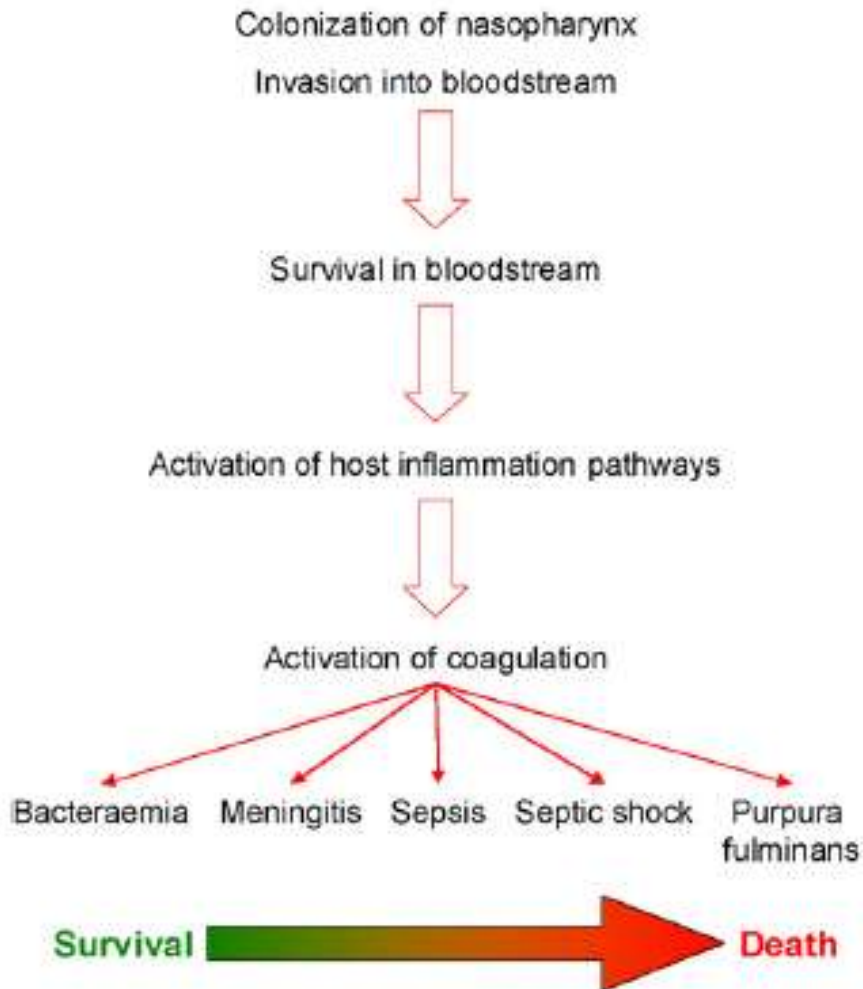
Pathway	Gene	Polymorphism	Su/Se/Ou	OR	Ref	Comments	
Innate immunity	TLR4	Asp299Gly	Su	No association	7		
			Su	OR 1-14 (0-86-1-52)	8		
			Se	OR 1-55 (0-70-3-44)			
	TLR2	Rare polymorphisms combined	Su	OR 27	7		
			Su	No association	7		
			Su	No association	7		
	LBP*	Multiple SNPs (no aa change)	Su	No association	7		
			Su	Only in male patients	9	No MD, sepsis in general	
	BPI*	Cys98Gly	Ou	Trend (low patient numbers)			
			Su	No association	9	No MD, sepsis in general	
			Su	Trend (low patient numbers)			
	ACE	Pro436Leu	Su	No association	9	No MD, sepsis in general	
			Ou	Trend (low patient numbers)			
	MBL1	A645G	Su	No association	9	No MD, sepsis in general	
			Su	No association	9	No MD, sepsis in general	
	MBL1	G545C	Su	No association	9	No MD, sepsis in general	
			Su	No association	9	No MD, sepsis in general	
	MBL1	PstI in intron 5	Su	No association	9	No MD, sepsis in general	
			Se	>ln DO	10		
	MBL1	284 bp insertion/deletion	Ou	14% >risk of mortality			
Su			OR 6-5 (2-0-27-2) (homozygous)	11			
MBL1	Codon 52 (Arg/Cys)	Se	OR 4-5 (0-9-29-1) (homozygous)				
		Se	OR 1-7 (1-1-2-6) (heterozygous)				
MBL1	Codon 54 (Gly/Asp)	Se	OR 2-2 (1-1-4-3) (heterozygous)				
		Se	OR 2-0 (1-3-3-0) (h+h+c)				
MBL1	Codon 57 (Gly/Glu)	Se	OR 2-4 (1-2-4-6) (h+h+c)				
		Se	Trend to less severe disease	11			
Properdin	C2061T (stop exon 4) type I	Su	RR 260	12			
		Se	RR 4-7-15	12			
Properdin	C2726T (stop exon 5) type I	Su	Increased mortality	12			
		Ou	Increased mortality	12			
Properdin	C3041G (stop exon 6) type I	Su	Increased mortality	12			
		Ou	Increased mortality	12			
Properdin	C2124T (Arg/Trp) type II	Su	Increased mortality	12			
		Ou	Increased mortality	12			
Properdin	G827A type II	Su	Increased mortality	12			
		Ou	Increased mortality	12			
Factor D	Codon 387 (Tyr/Asp) type III	Su	Increased mortality	12			
		Ou	Increased mortality	12			
C3	Ser42 stop	Su	Increased	13	Case report		
		Ou	Increased	13	Case report		
LOCD	Different defects	Su	Increased (57-71%)	12			
		Se	Decreased	12			
Acquired immunity	FcyRIIa	His131Arg	Se	His: sepsis	14		
			Su	Arg: meningitis	15		
			Se	No association	15		
			Su	Arg: OR 3-9 (1-0-16)	15		
			Su	OR 2-67 (1-09-6-53)	16	Only 25 survivors of MD studied	
	FcyRIIa	Val158Phe	Se	Arg: OR 14	17	LOCD patients	
			Se	Val: meningitis	14	Relatives of patient	
	FcyRIIb	NA1/NA2 (codon 65 and 82)	Su	No association	16		
			Su	OR 2-6 (1-1-6-3)	14	Relatives of patient	
	Combination	RR-FF-NA2/2	Su	OR 13-9	18,19	LOCD patients	
			Su	RR-NA2/2	19	Properdin deficient individuals	
	Coagulation/fibrinolysis	IPA	Alu repeat insertion/deletion	Su	No association	20	
				Se	No association	20	
				Su	No association	21,22	
				Ou	RR 4/4G 2-0 (1-0-3-8)	21,22	
Se				OR 4/4G 5-9 (1-9-18)	22	Relatives of patient	
PAI1		4G/5G insertion/deletion	Ou	No association	23	Relatives of patient	
			Su	No association	23		
PAI1		4G/5G insertion/deletion	Se	4/4G twofold increase	23	Predicted mortality	
			Se	R/R 4/4G 2-4	23	Vascular complications in survivors in meningococcal sepsis patients	
PAI1		4G/5G insertion/deletion	Ou	RR 2-7	23		
			Su	No association	24		
Factor V		FV G1691A	Se	RR 3-1 (1-2-7-9) (heterozygous)	24		
			Ou	No association	24		
Cytokines		TNFα	G-308A	Su	No association	25	No MD, sepsis in general
				Se	RR 1-6 (1-1-2-3)	25	
	Ou			RR 2-5 (1-1-5-7)	25	Relatives of patients	
	TNFα	G-308A	Ou	No association	26		
			Ou	No association	27		
	TNFα	G-238A	Ou	No association	26	Relatives of patients	
			Ou	B2 increased mortality	28	No MD, sepsis in general	
	TNFβ	NcoI B1+, B2-	Ou	OR 3-47	29	No MD, sepsis in general	
			Ou	OR 3-47	29	No MD, sepsis in general	

INFEZIONE DA MENINGOCOCCO



INFEZIONE DA MENINGOCOCCO

Course of meningococcal disease

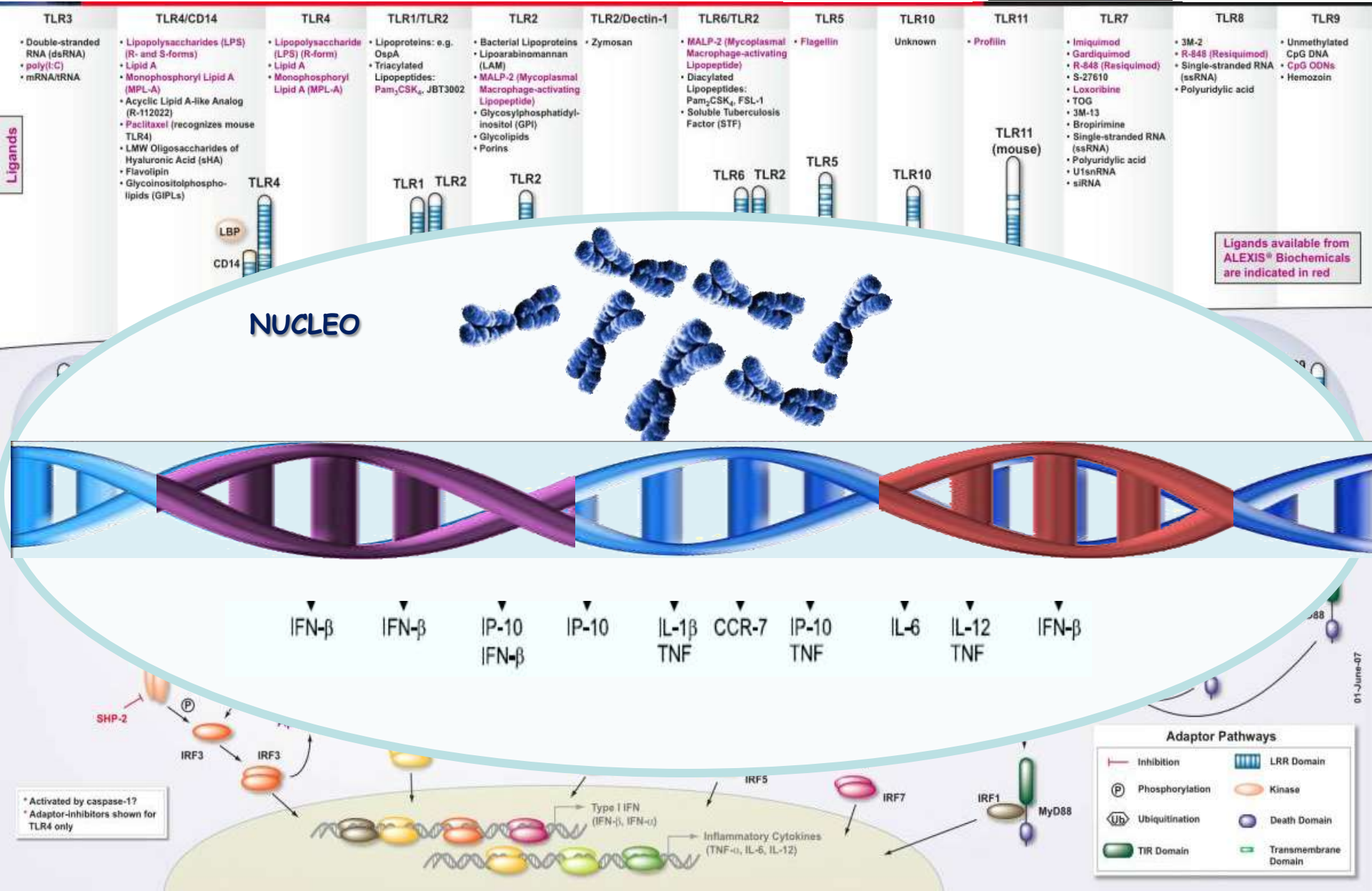


Sites of genetic control

- Epithelial surface
- ABO secretion status
- Adhesion molecules
- Complement, Antibody, Innate prote
- Pattern recognition receptors
- NF- κ B pathway
- Clotting factors, Thrombolysis
- Coagulation inhibitors
- Cytokines
- Inflammatory mediators

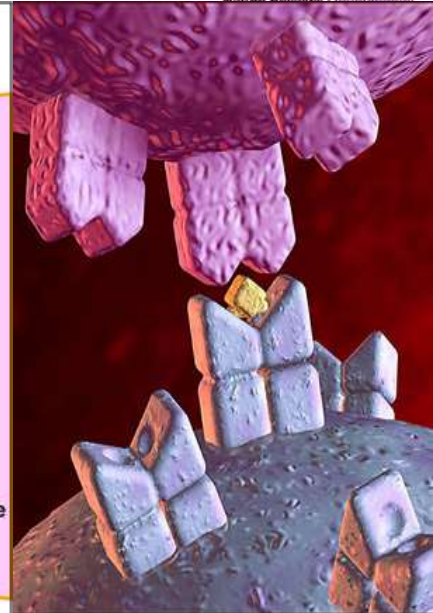
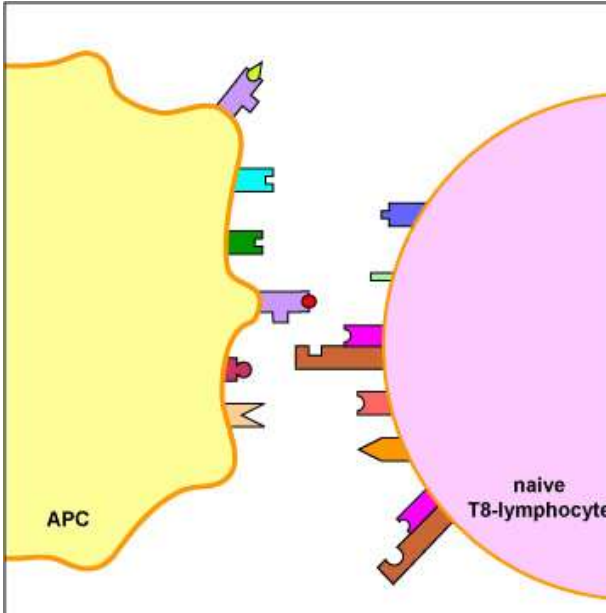
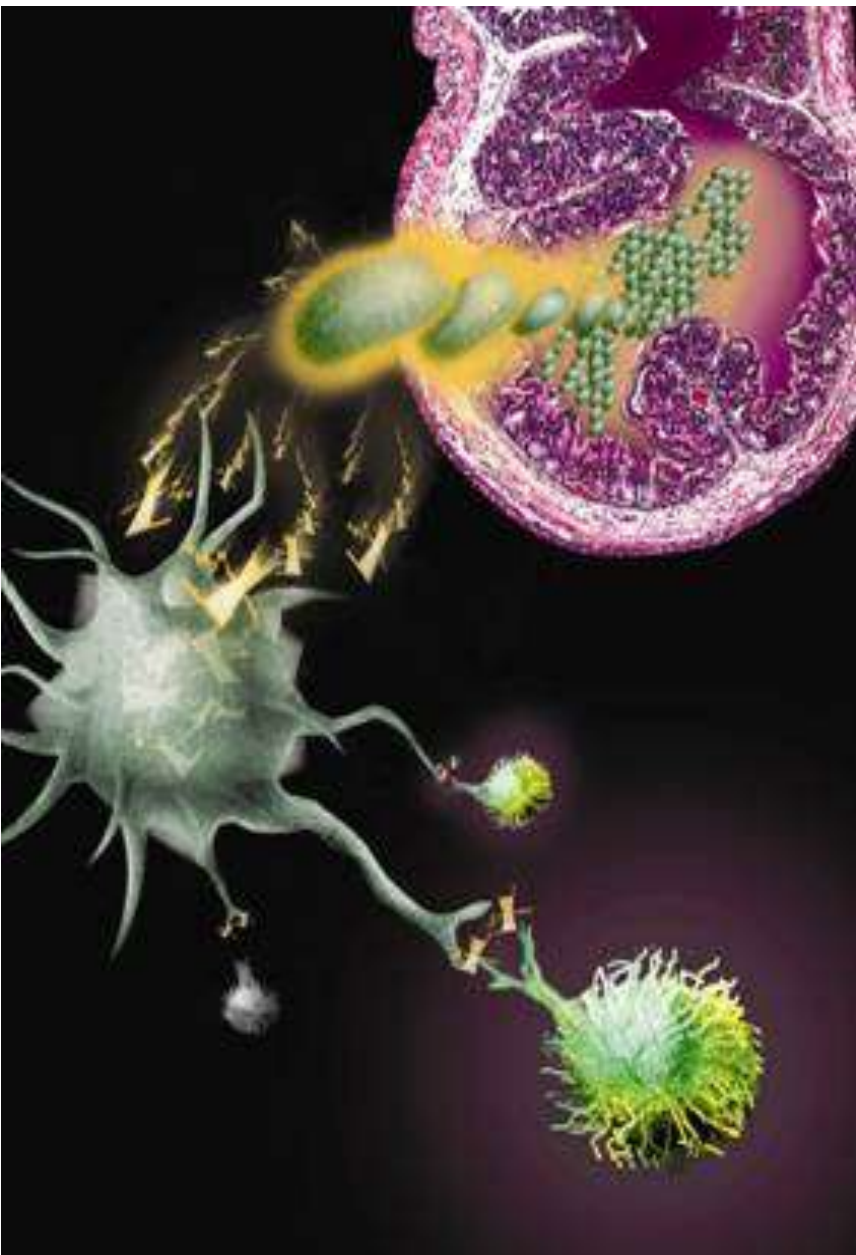
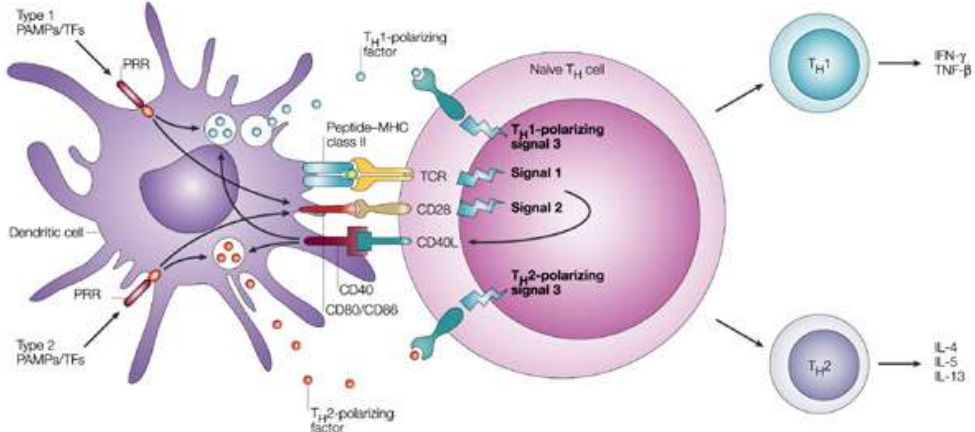


ANTIGENI E TLR

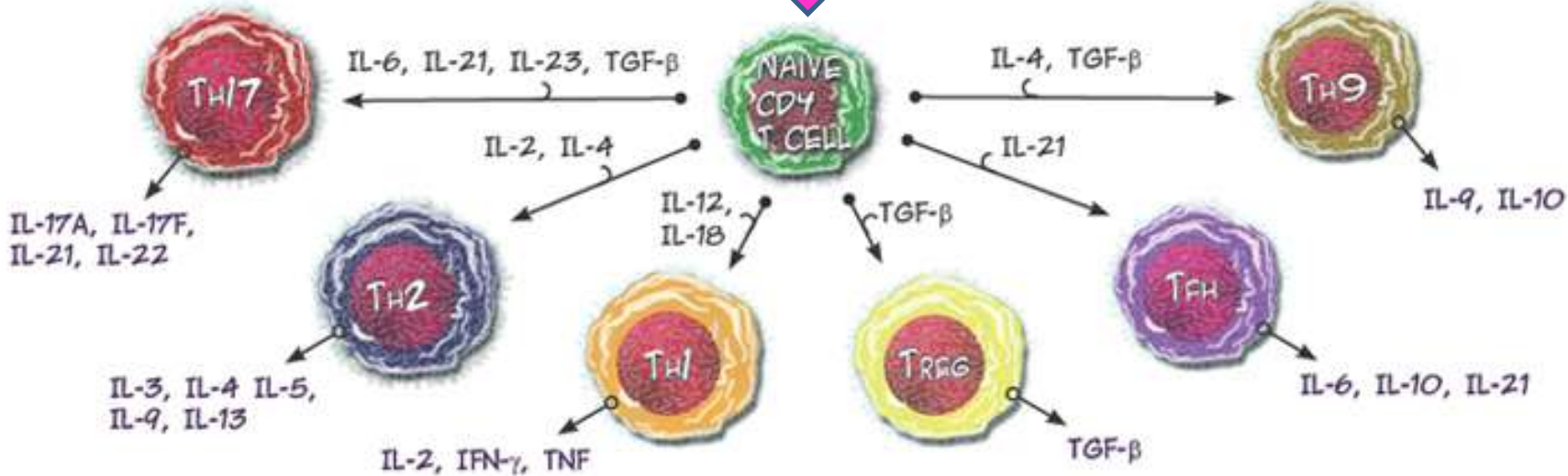
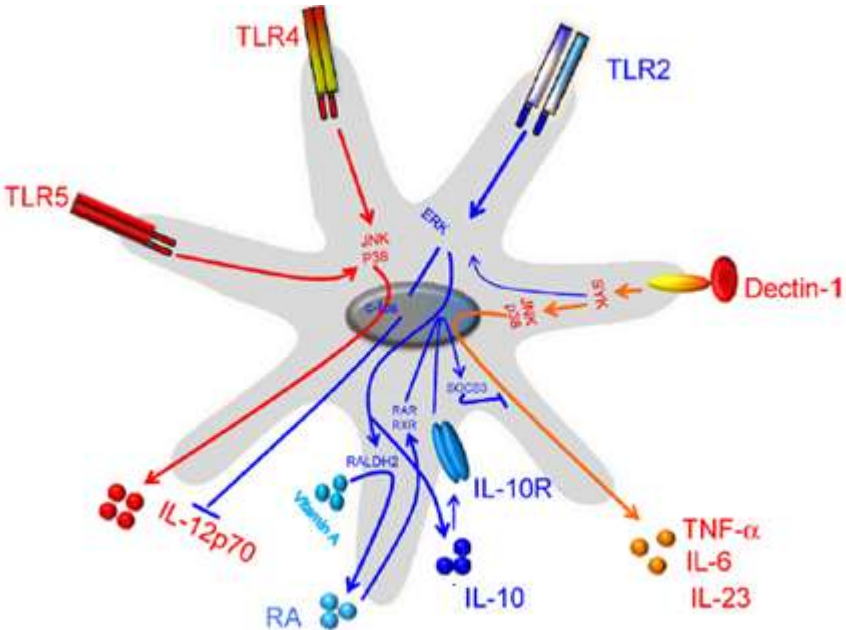


* Activated by caspase-1?
* Adaptor-inhibitors shown for TLR4 only

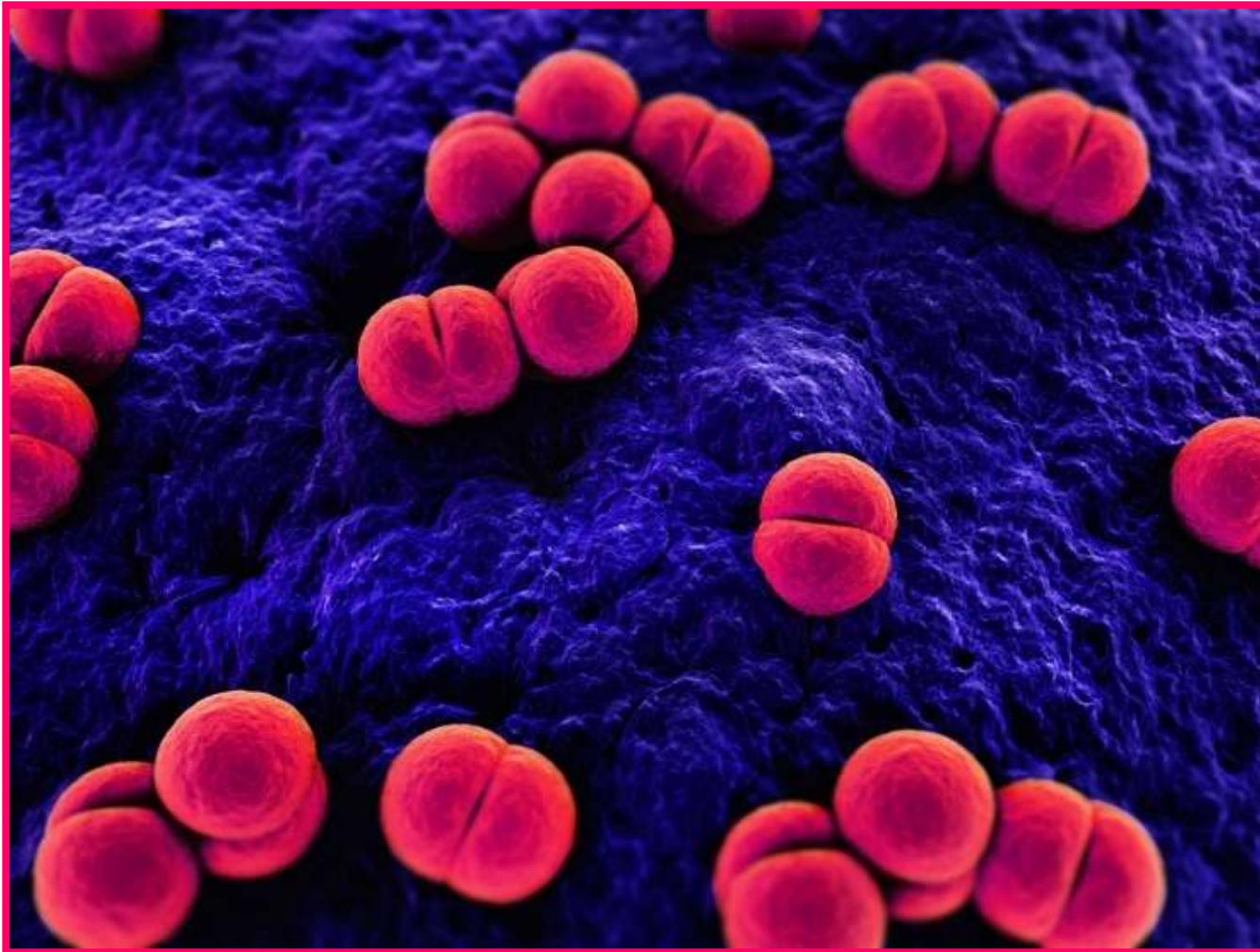
INTERAZIONE CELLULA DENDRITICA/LINFOCITA



DINAMICA EVOLUTIVA T CELLS



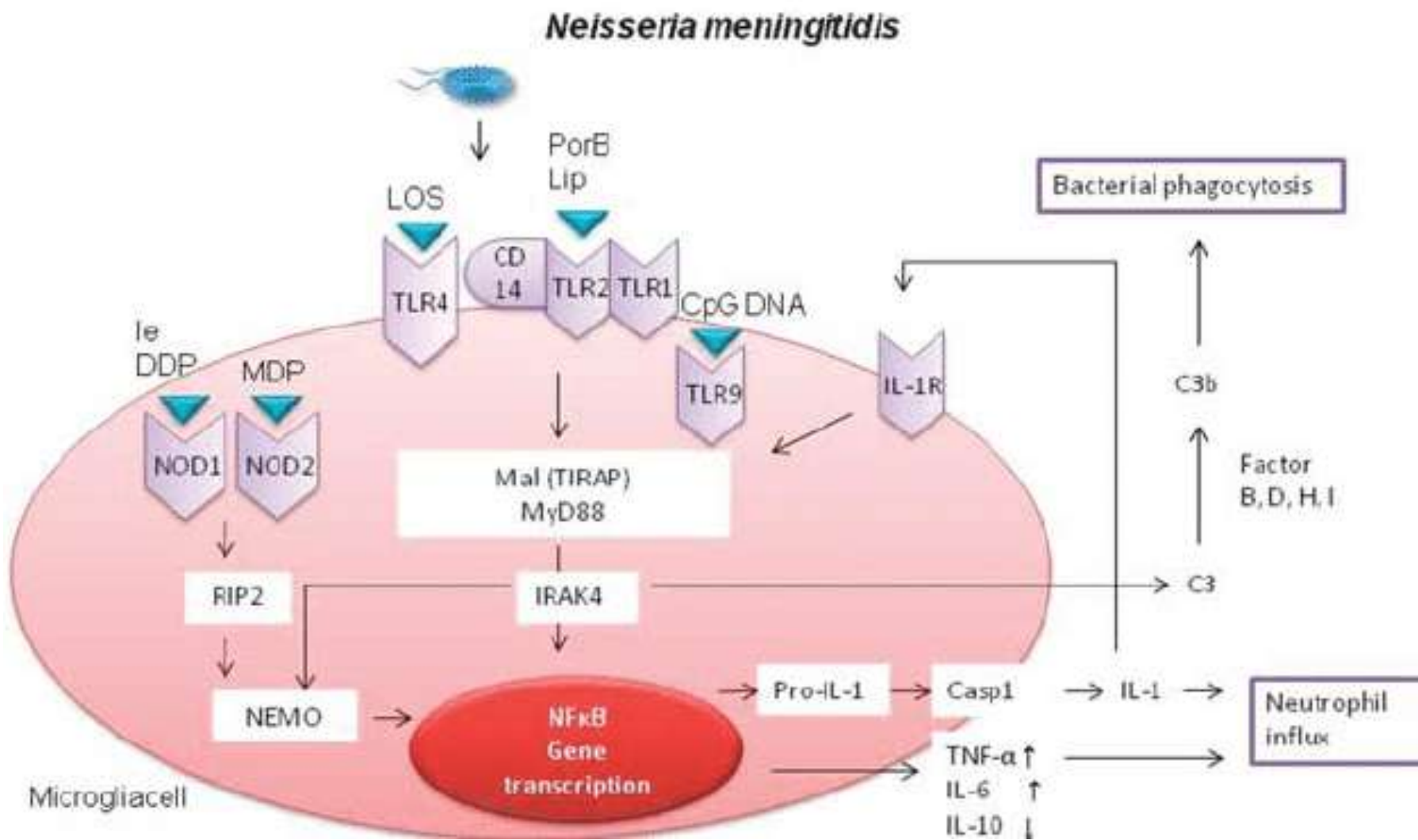
NEISSERIA MENINGITIDIS



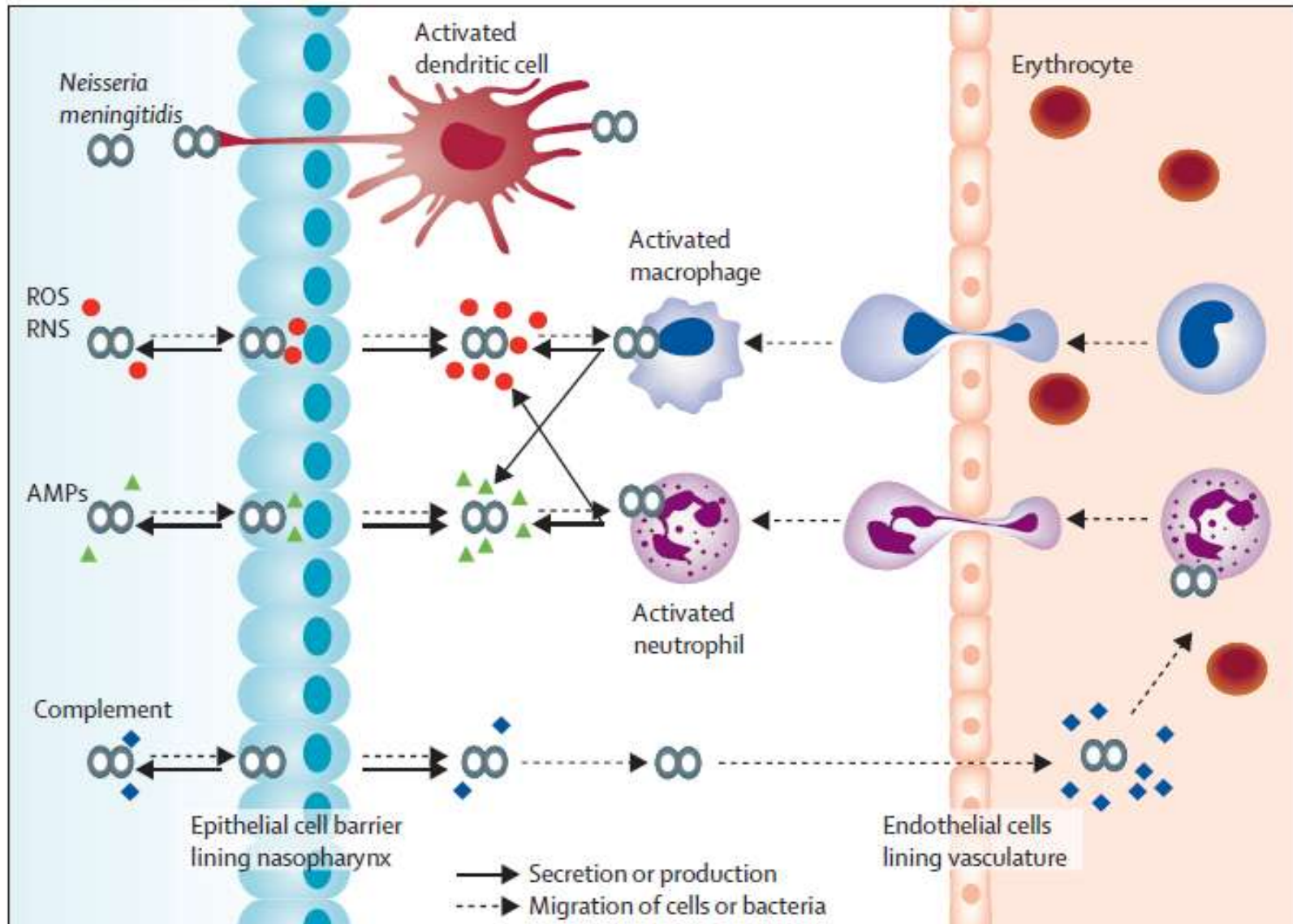
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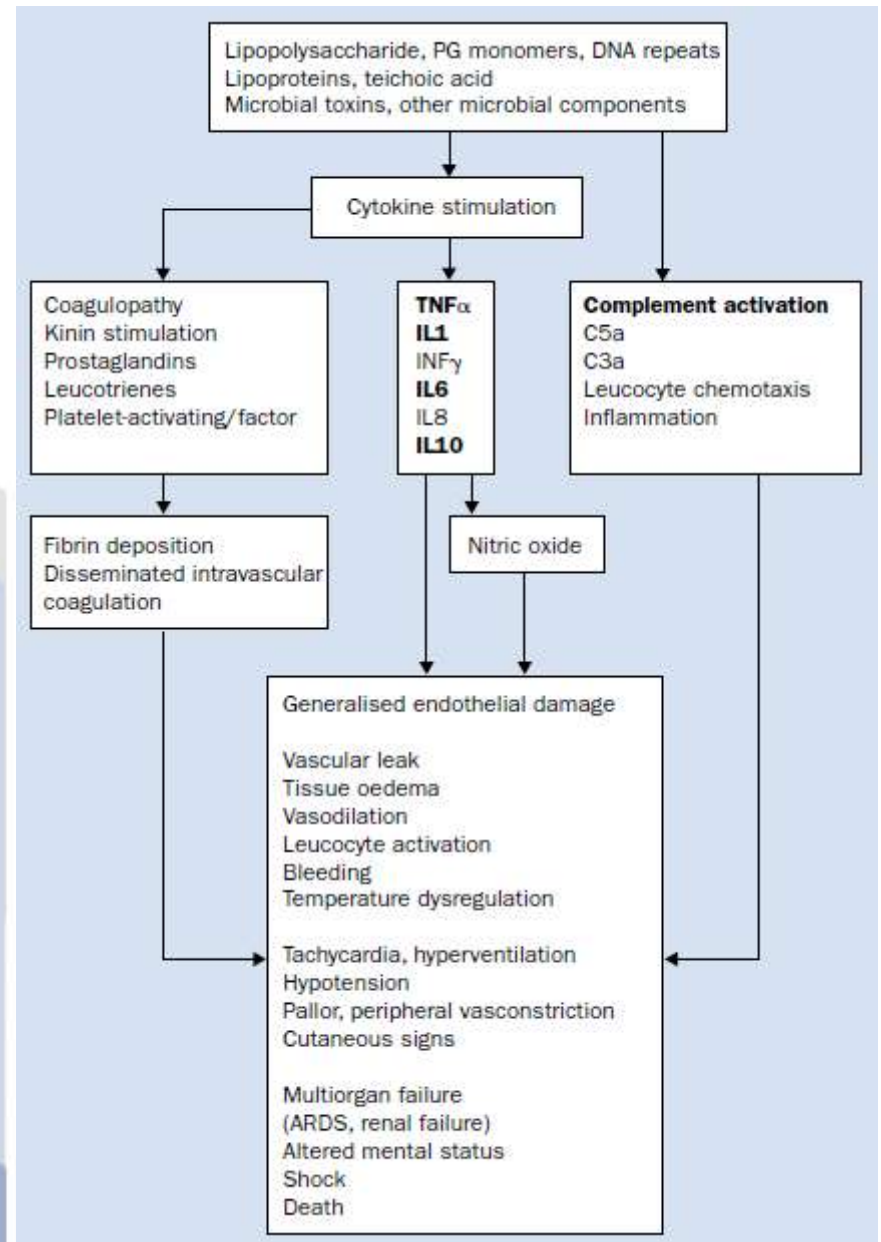
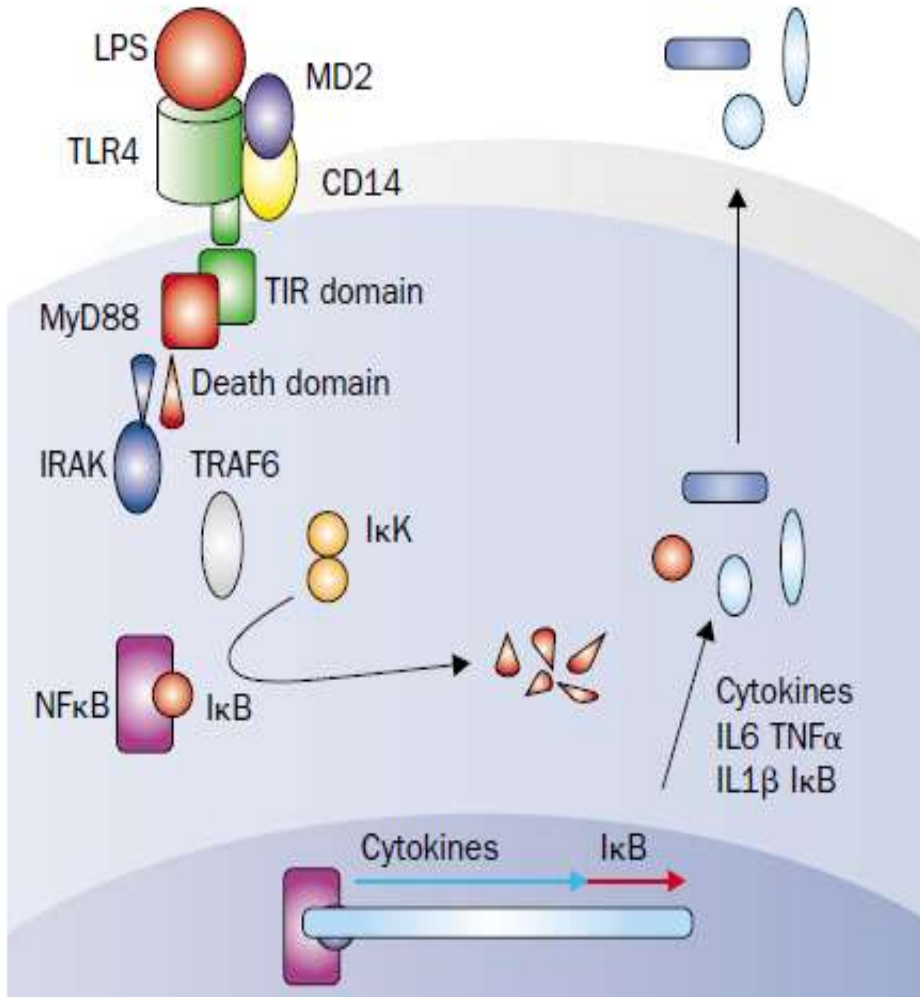
RISPOSTA IMMUNITARIA INNATA CONTRO LA *NEISSERIA MENINGITIDIS*



RISPOSTA IMMUNITARIA INNATA CONTRO LA *NEISSERIA MENINGITIDIS*



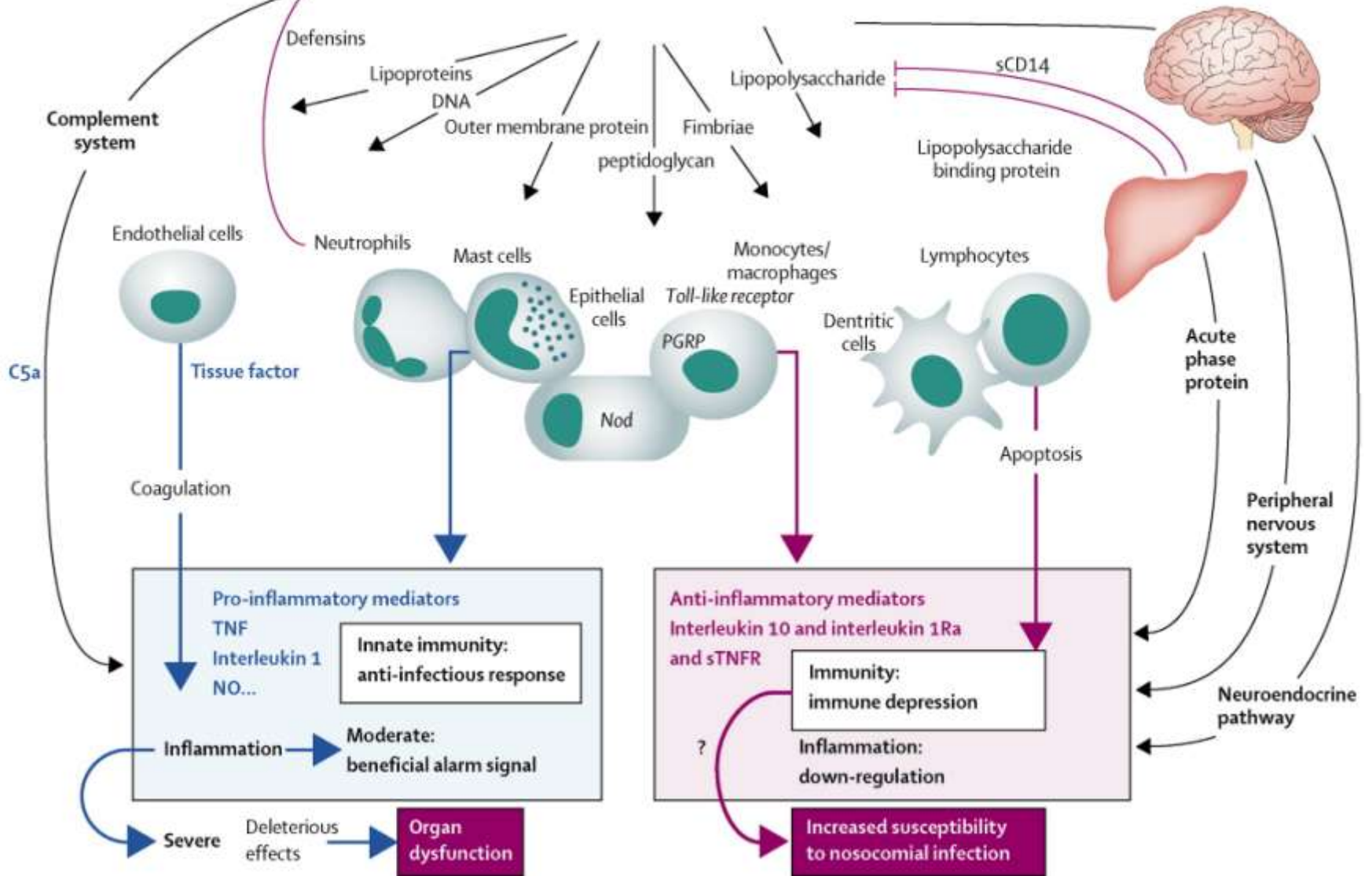
CASCATA INFIAMMATORIA INNESCATA DAL MENINGOCOCCO



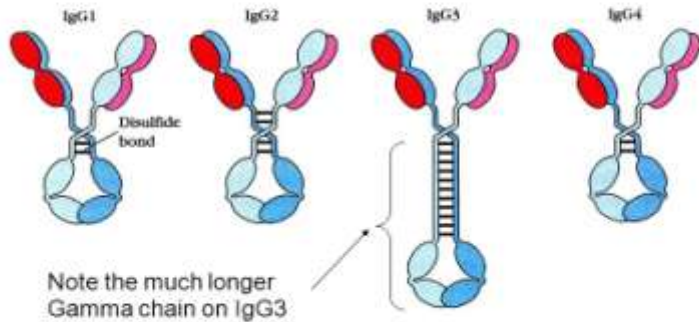
INFECTION

Bacteria

SEPSIS



Four Subclasses of IgG

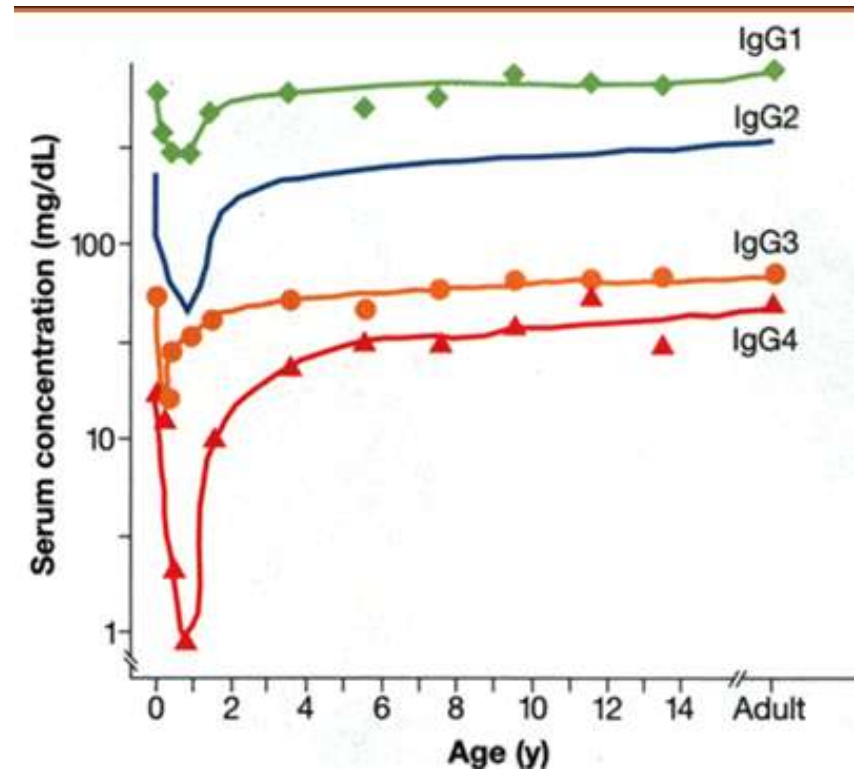


DEFICIT SOTTOCLASSI IgG

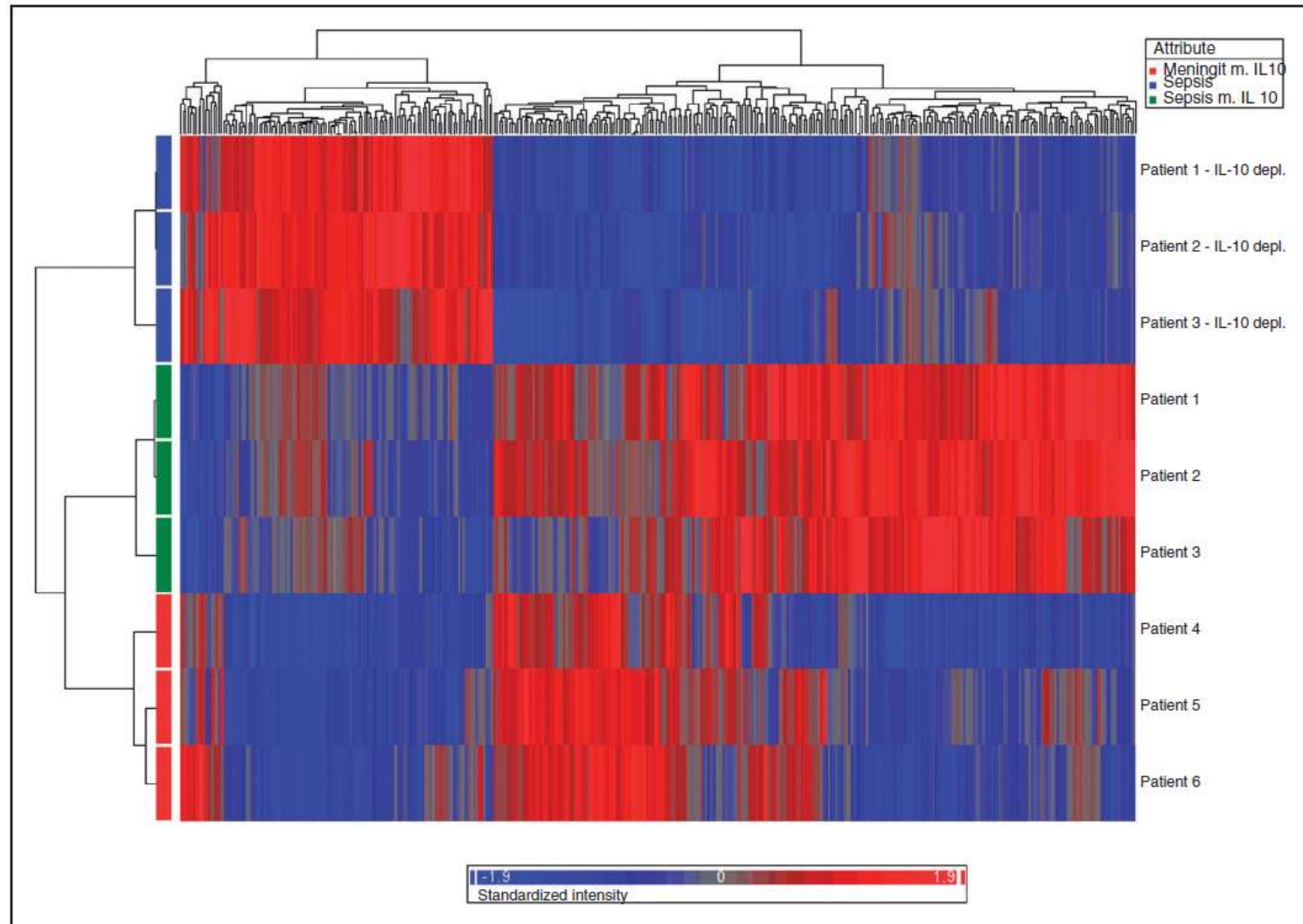
Function	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Neutralization	+	-	+++	+++	+++	+++	+++	-
Opsonization	-	-	+++	*	++	+	+	-
Sensitization for killing by NK cells	-	-	++	-	++	-	-	-
Sensitization of mast cells	-	-	+	-	+	-	-	+++
Activation of complement system	+++	-	++	+	+++	-	+	-

Property	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Transport across epithelium	+	-	-	-	-	-	+++ (dimer)	-
Transport across placenta	-	-	+++	+	++	++	-	-
Diffusion into extravascular sites	+/-	-	+++	+++	+++	+++	++ (monomer)	+
Mean serum level (mg/ml)	1.5	0.03	9	3	1	0.5	2.5	5×10^{-5}

Figure 4.32 The Immune System, 3ed. © Garland Science 2009



INFEZIONE DA N.M.: 373 GENI DELLA "HEATMAP" REGOLANO LA DIFFERENTE RISPOSTA DELLA IL10



Articolo in press 2017

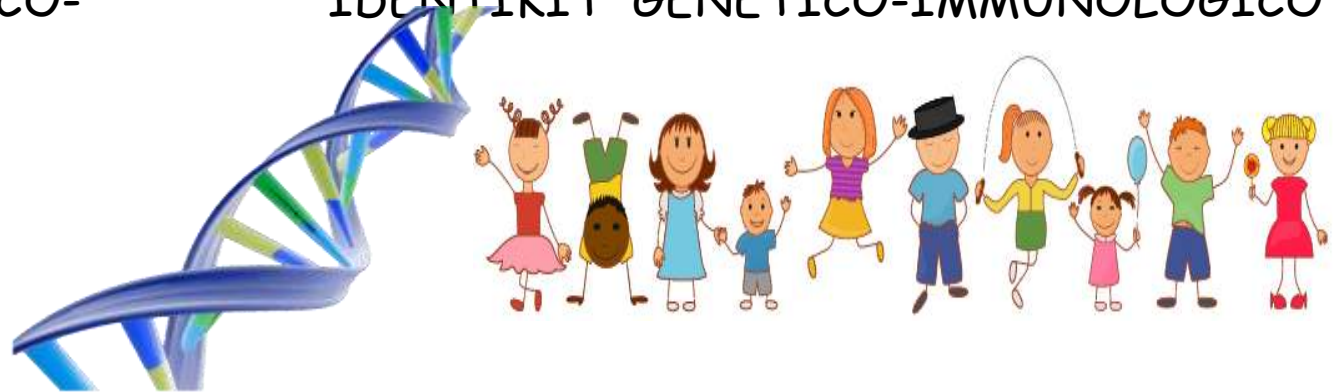
BATTERIO

OSPITE

IDENTIKIT GENETICO-MICROBIOLOGICO



IDENTIKIT GENETICO-IMMUNOLOGICO



RISPOSTA DELL'OSPITE

RISPOSTA
IMMUNOLOGICA
EFFICACE

BATTERIEMIA
SENZA SEPSI

DANNO
VASCOLARE/TISSUTALE/
DIC/SHOCK

MENINCOCCEMIA
SENZA MENINGITE

BARRIERA
EMATOENCEFALICA
ALTERATA

MENINGITE CON O SENZA
MENIGOCCEMIA

MENINGITE BATTERICA ACUTA-SEGNI E SINTOMI



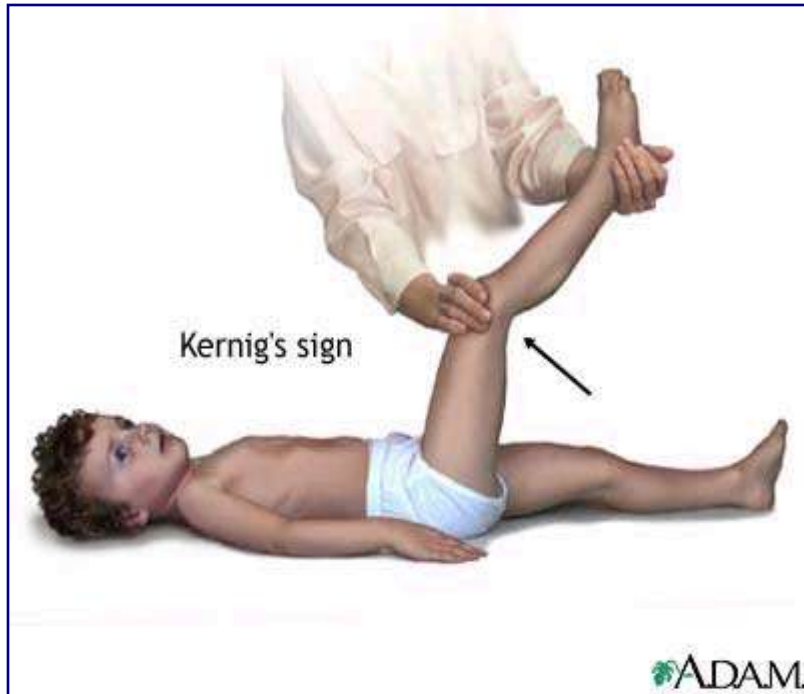
- Cefalea
- Fotofobia
- Allucinazioni
- Rachialgie
- Vomito a getto

SINTOMI

- Febbre
- Meningismo
- Posizione a "cane di fucile"
- Alterazioni stato mentale
- Paralisi nervi cranici
- Convulsioni
- Papilledema
- Deficit neurologici focali

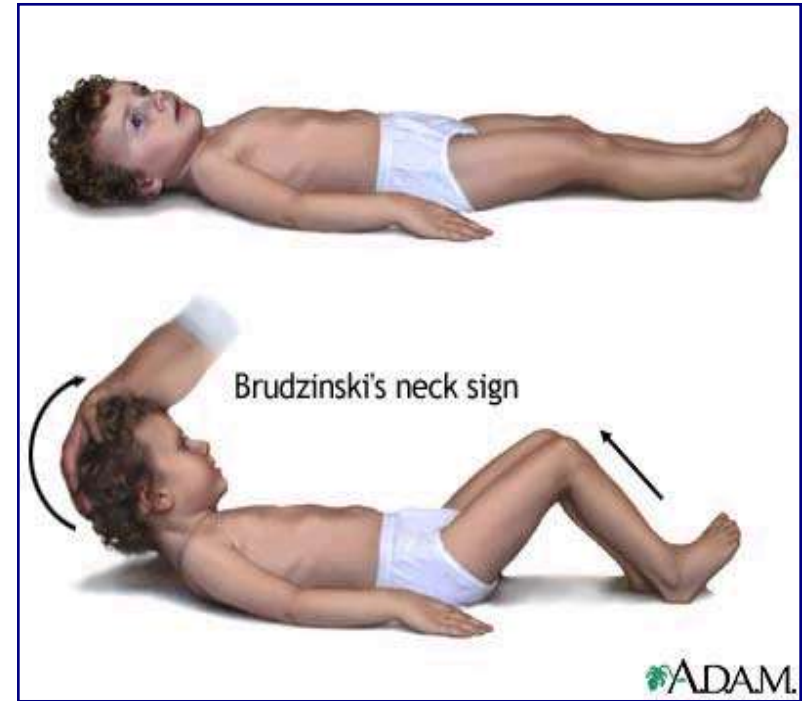
SEGNI

SEGNI OBIETTIVI



SEGNO DI KERNIG

L'estensione del ginocchio risulta dolorosa e difficoltosa. La resistenza alla estensione provoca flessione del ginocchio controlaterale



SEGNO DI BRUDZINSKI

a paziente supino con estremità estese si flette il collo. La flessione risulta difficoltosa e provoca la flessione delle gambe

RIGIDITÀ NUCALE
POSIZIONE A CANE DI FUCILE

INFEZIONI DA N.M.: TIPICA EVOLUZIONE TEMPORALE DEL QUADRO CLINICO DALL'ESORDIO DEI SINTOMI CLINICI

SINTOMI PRECOCI (4-8 ore)

- Irritabilità
- Inappetenza
- Febbre
- Nausea
- Mal di gola

SINTOMI CLASSICI (12-15 ore)

- Rash emorragico
- Meningismo
- Fotofobia

SINTOMI TERMINALI (15-~24 ore)

- Confusione/delirio
- Convulsioni
- Perdita di coscienza
- Shock settico
- Possibile decesso



Febbre



Rigidità Nucale



Sensibilità alla luce



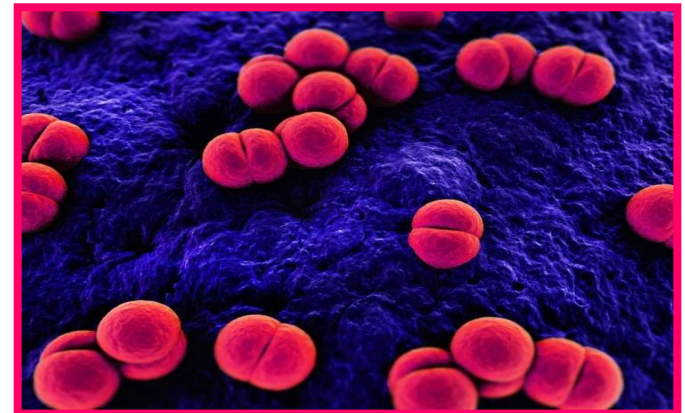
Nausea/Vomito



Malessere Generale



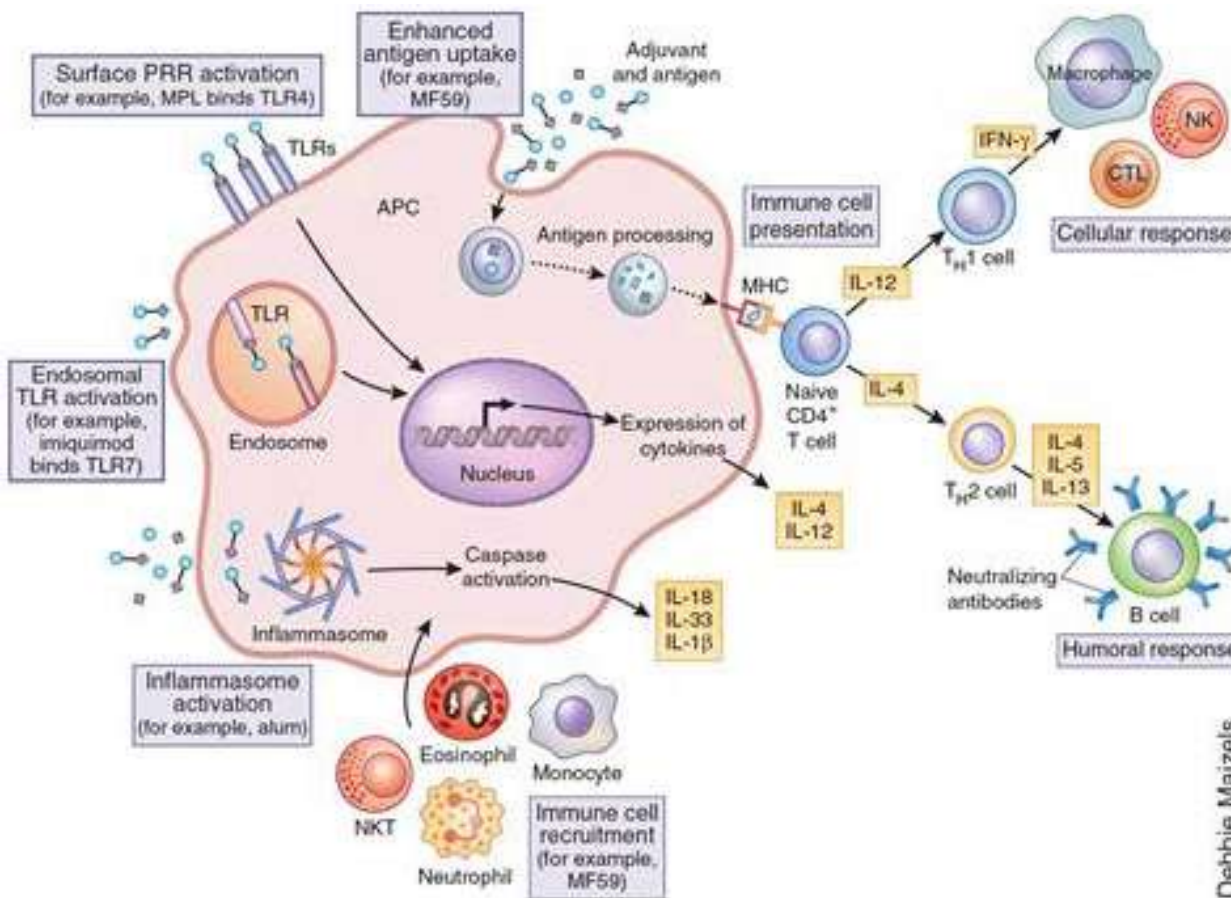
Rash Cutaneo



La Meningite Meningococcica è la malattia invasiva più grave prevenibile con la vaccinazione

Malattia	Tasso di letalità	Note
Ebola ¹	50%–89%	
H5N1 (influenza aviaria)	59%	Casi riportati in Africa e Asia 2003–2010
Vaiolo	≥30%	Considerato eradicato nel 1980
Malattia meningococcica invasiva	9%–12%	A dispetto di appropriato trattamento antibiotico
Difterite ⁴	5%–10%	
Pneumococcal pneumonia ⁴	5%–7%	
Polio paralitica ⁴	2%–5%	
Meningite da Hib ⁴	2%–5%	
Varicella ⁴	<1%	Bambini e adolescenti
Morbillo ⁴	0.2%	United States, 1985–1992
Rotavirus ⁵	0.01%	US

POSSIBILI MECCANISMI DI AZIONE DELL' ADIUVANTE

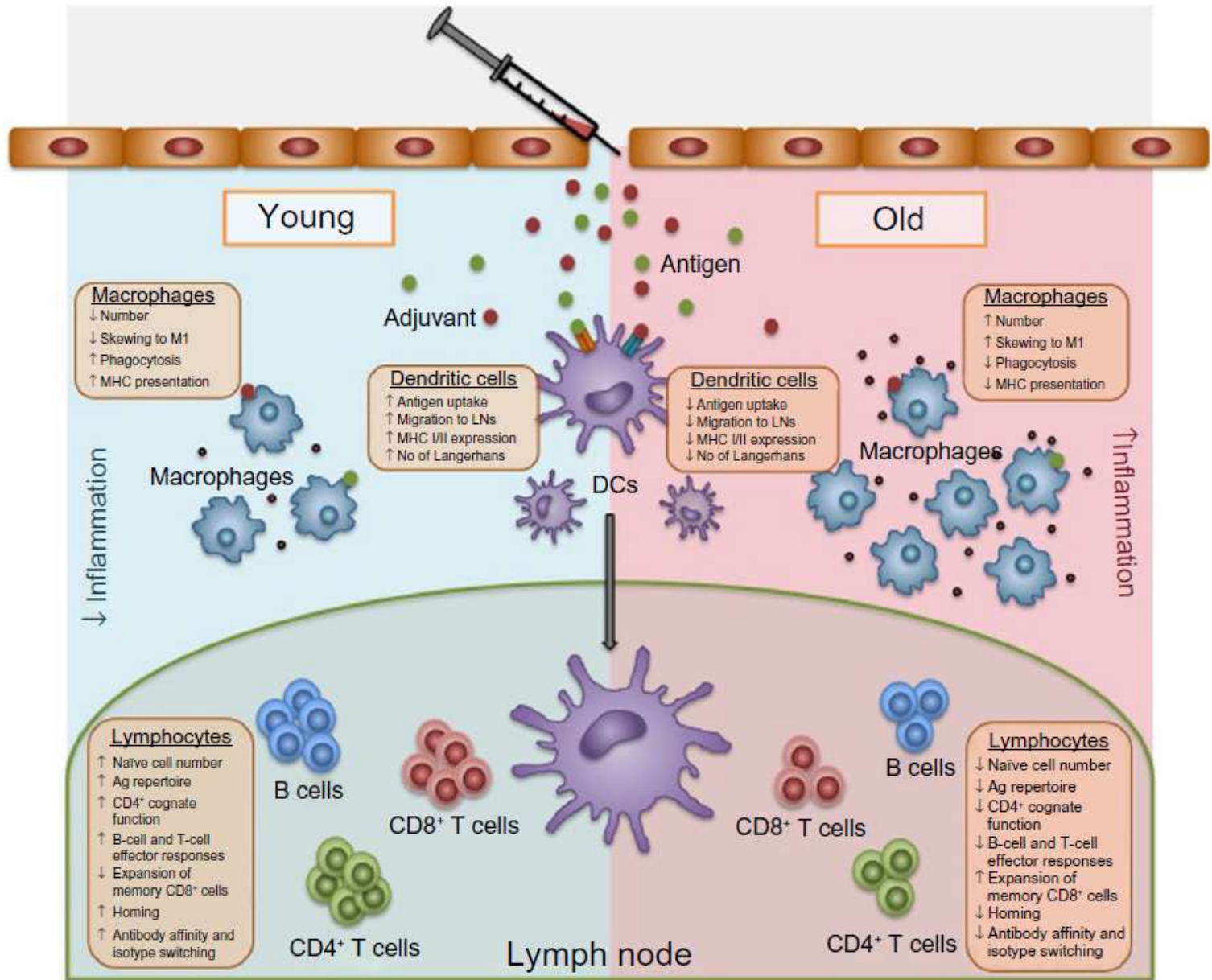


duced intermediate responses. However, some formulations at certain doses may not

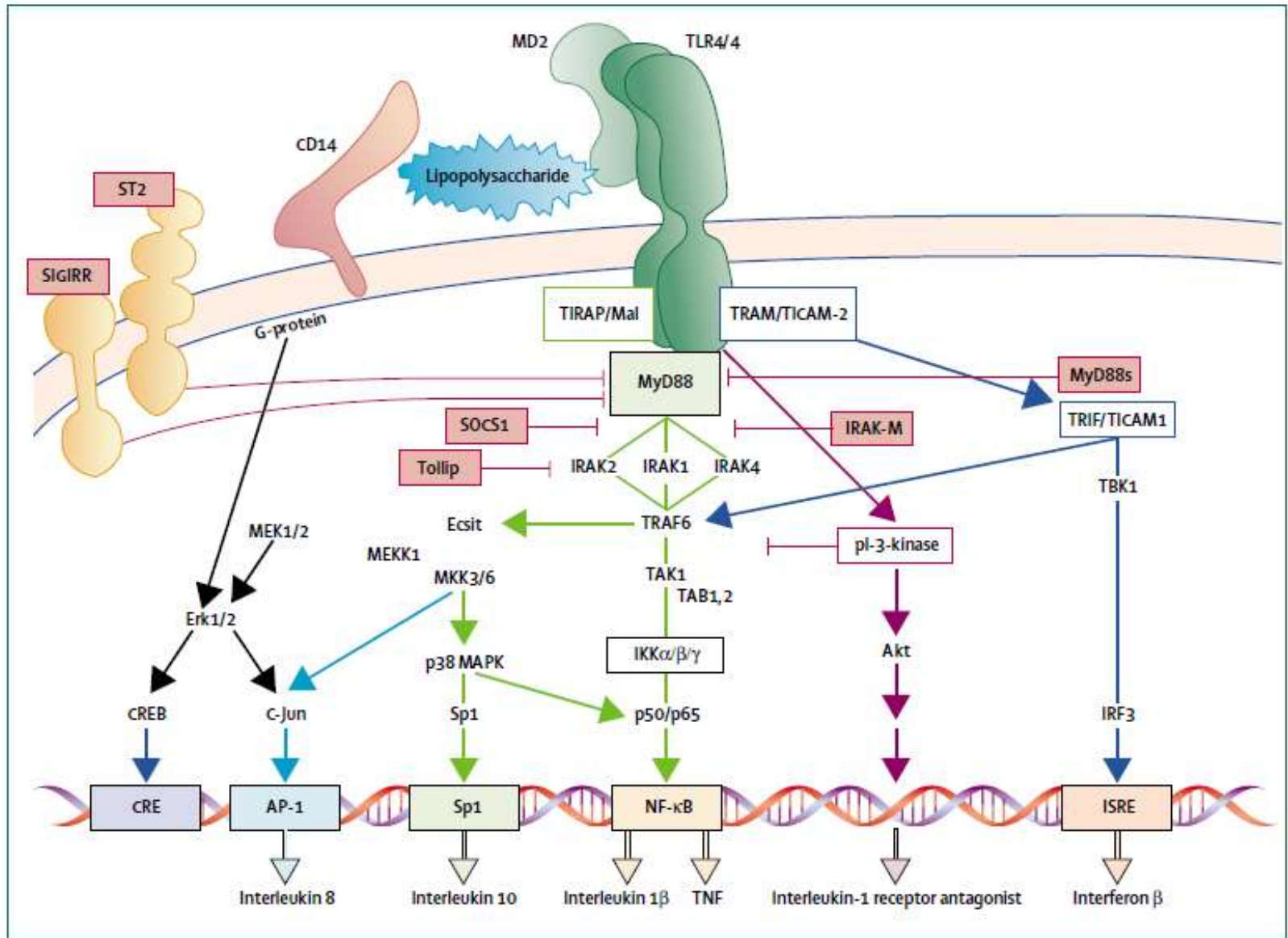
Figure 4 Putative mechanisms of action of adjuvants. A number of mechanisms have been postulated through which adjuvants mediate their activity. Many adjuvants can act as ligands for PRRs that activate an innate immune response. Receptor signaling can then activate transcription factors that induce the production of cytokines and chemokines that help direct a particular immune response, such as a T_H1 or T_H2 type response, as well as influence the immune cells that are recruited to the site of injection. Inflammasome activation has also been implicated as a mechanism for some adjuvants. Activation of the inflammasome leads to the production of the proinflammatory cytokines IL-1β and IL-18. Some adjuvants also influence antigen presentation by MHC. It is possible that some adjuvants can act through multiple mechanisms; for example, it has been suggested that alum can affect antigen uptake, PRR signaling, inflammasome activation and recruitment of immune cells, NK, natural killer cell.

Debbie Maizels

DIFFERENTE RISPOSTA VACCINALE PER ETA'



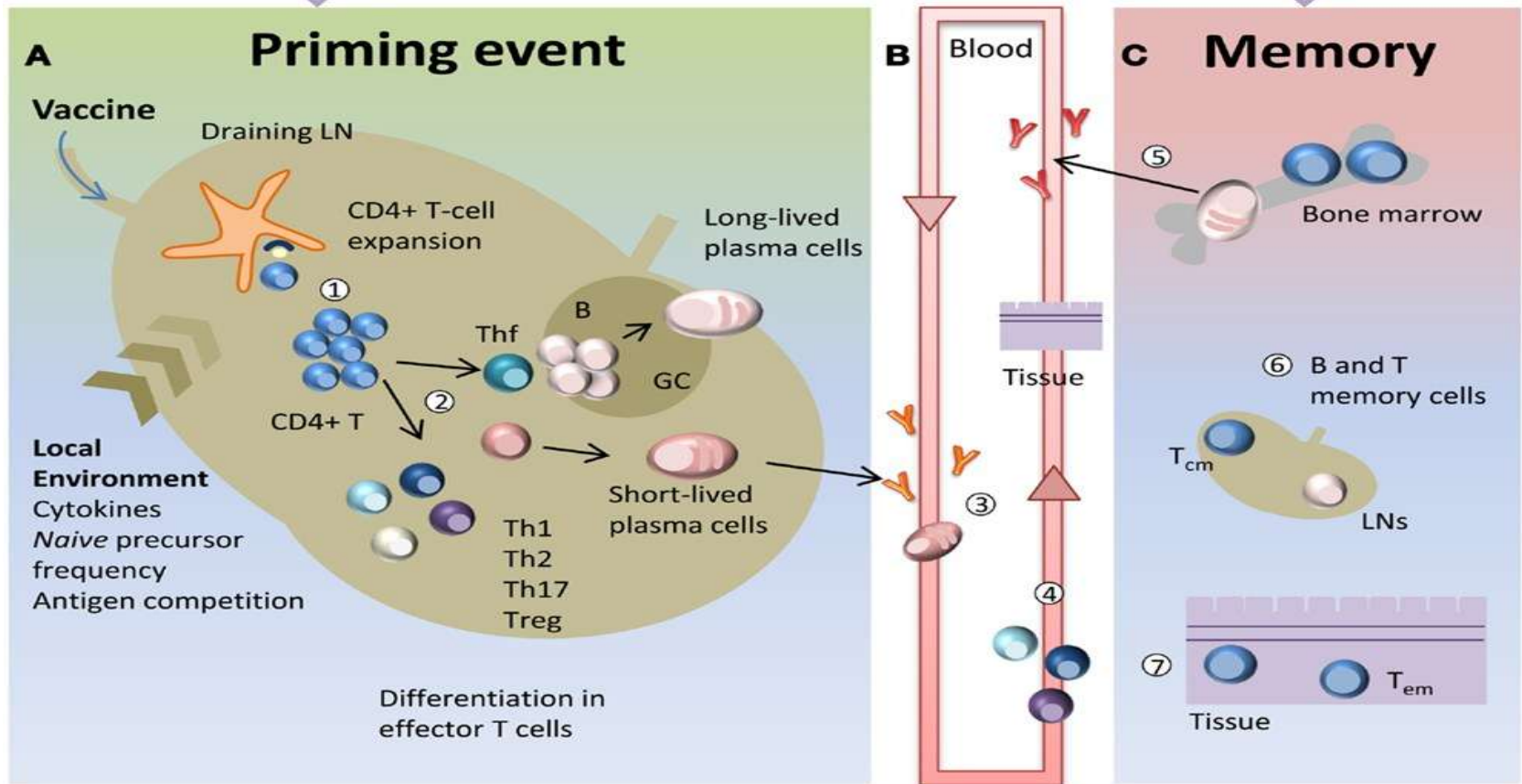
RISPOSTA IMMUNOLOGICA



Priming

Boosting

Formulation (Delivery system/Adjuvant)
Antigen dose
Route



Reduction in *Neisseria meningitidis* infection in Italy after Meningococcal C conjugate vaccine introduction: A time trend analysis of 1994–2012 series

Chiara de Waure¹, Alessandro Miglietta^{2,*}, Darko Nedovic³, Giovanna Mereu², and Walter Ricciardi¹

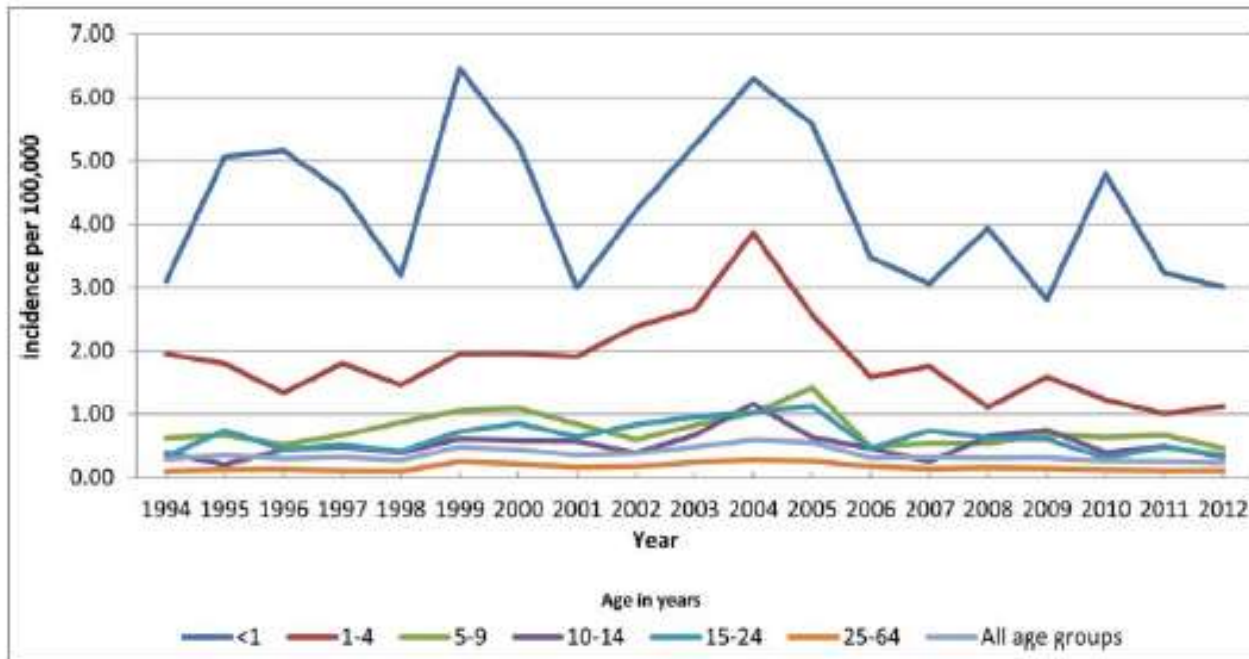


Figure 1. incidence of IMD (per 100,000) by age group in Italy - 1994–2012.

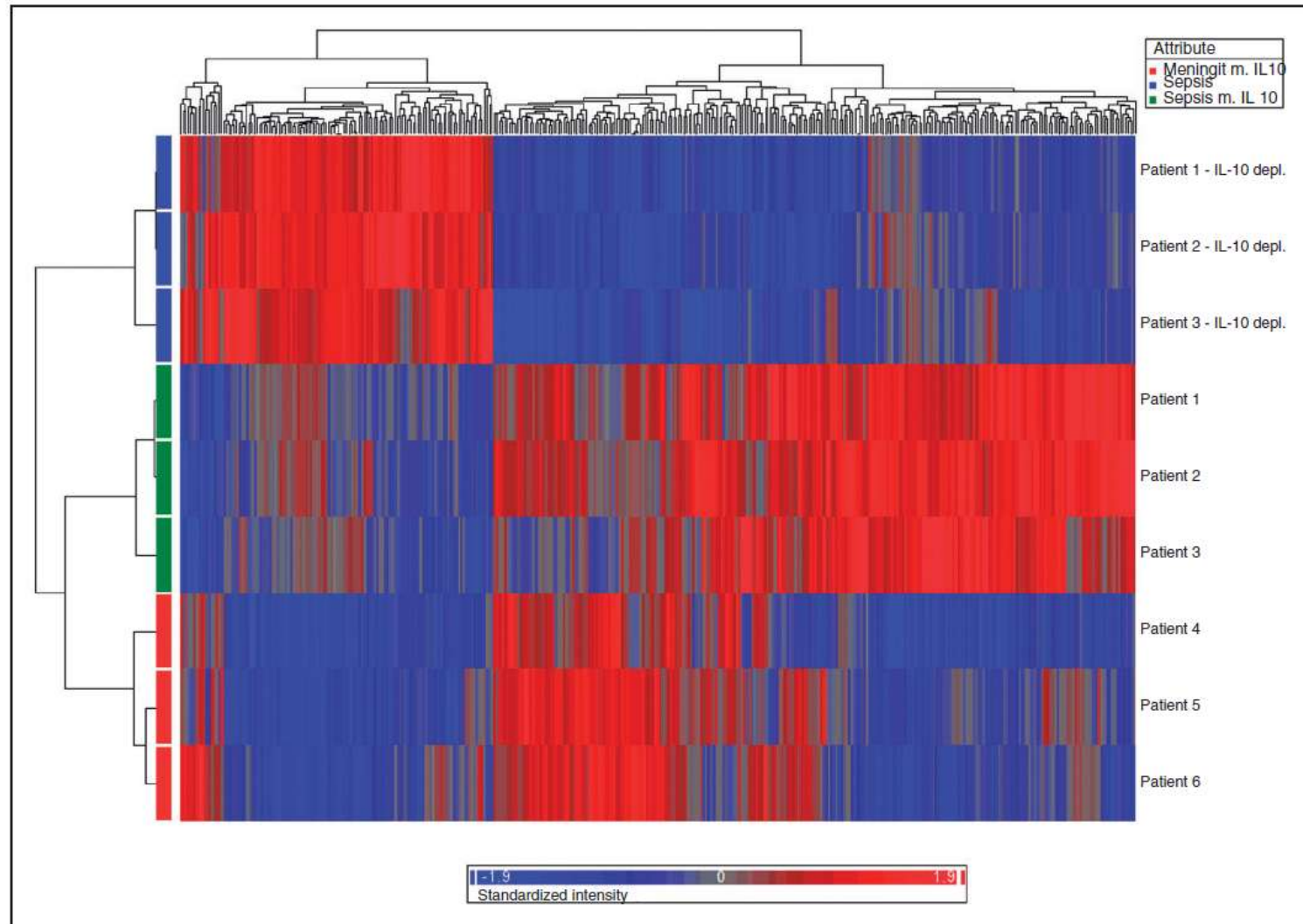
AURORA, 3 anni



A tre giorni di distanza dalla somministrazione di vaccino anti-MenC comparsa di febbre e di manifestazioni cutanee eritemato-pomfoidi a carattere nonorragico

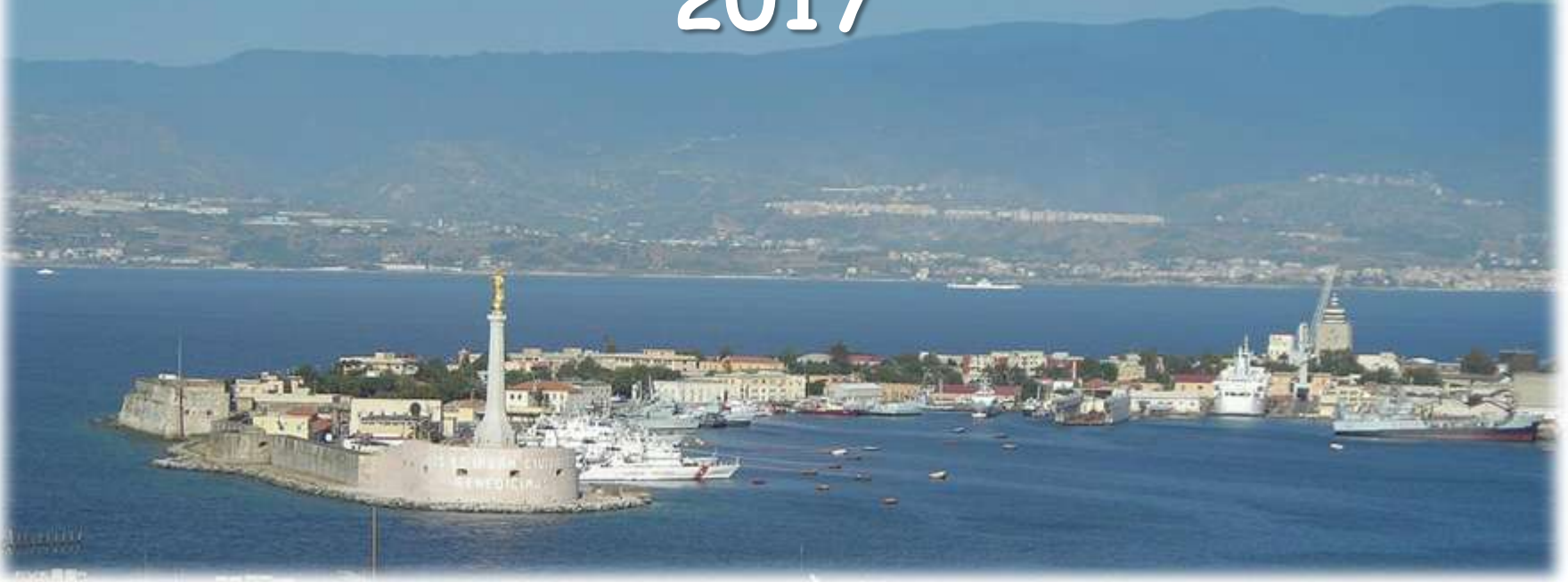


INFEZIONE DA N.M.: 373 GENI DELLA "HEATMAP" REGOLANO LA DIFFERENTE RISPOSTA DELLA IL10



Articolo in press 2017

I Percorsi Pediatrici dello Stretto 2017



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SABATO 25 MARZO 2017

SABATO 22 APRILE 2017

SABATO 20 MAGGIO 2017