

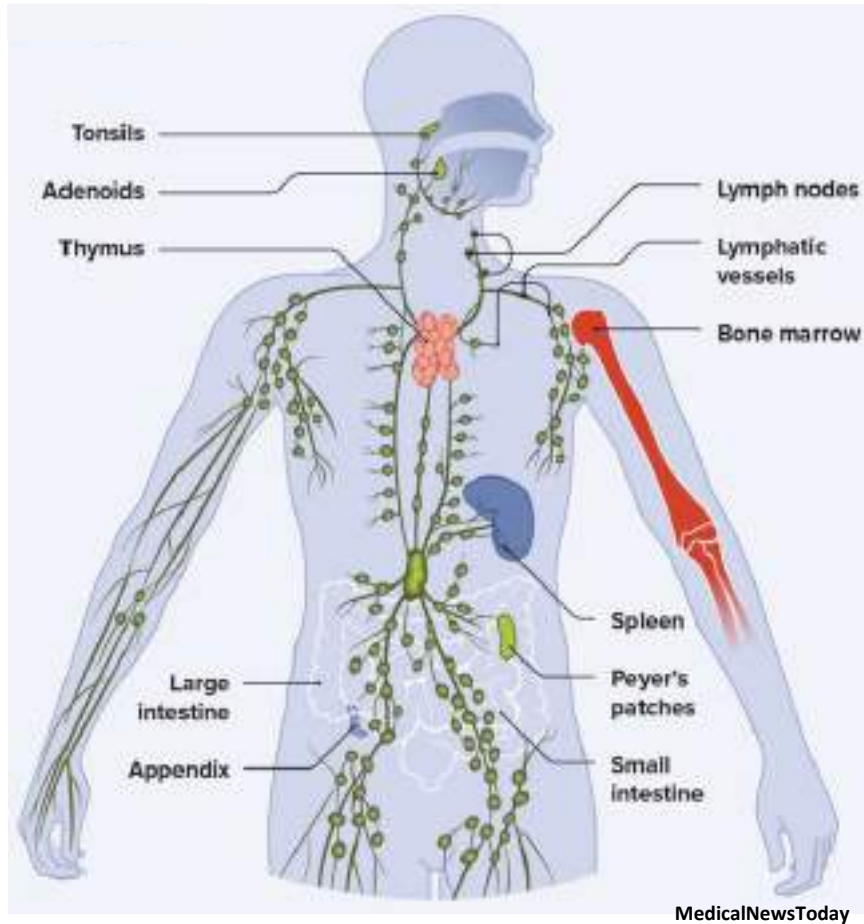


Evoluzione del Sistema Immunitario nelle diverse fasce d'età: immunità innata ed adattativa

Davide Zella, PhD

- Assistant Professor of Biochemistry and Molecular Biology
- Co-Head, Laboratory of Tumor Cell Biology
- Institute of Human Virology
- University of Maryland, School of Medicine

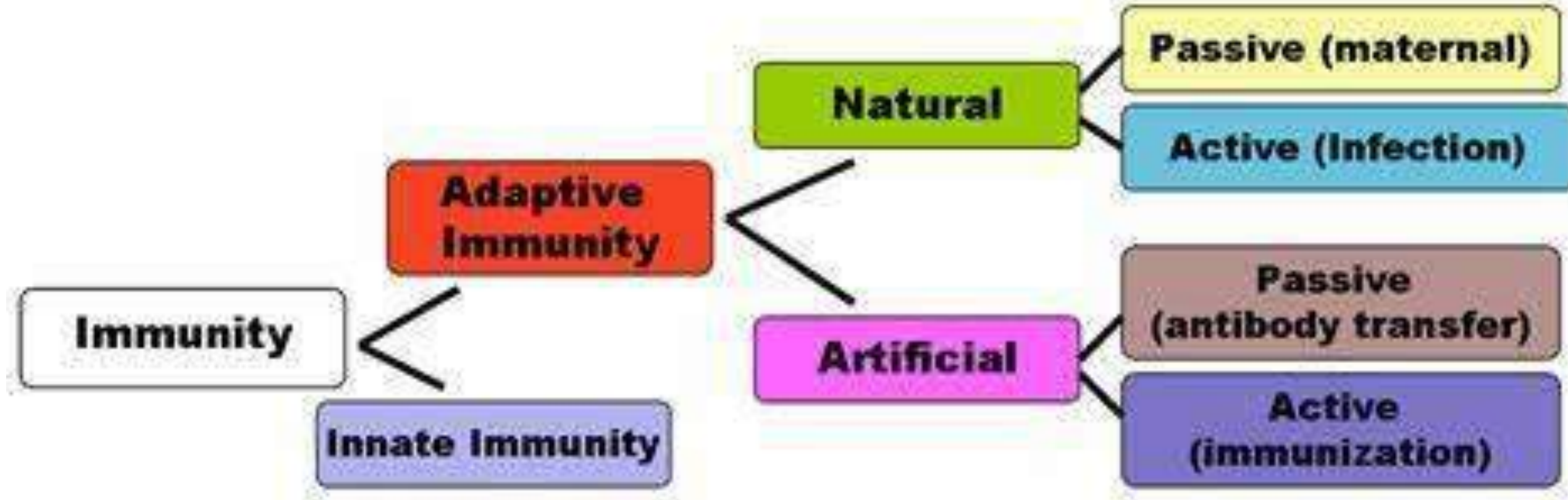
Il Sistema Immunitario: concetti generali



Principali organi componenti il Sistema Immunitario

Tipi di Immunità

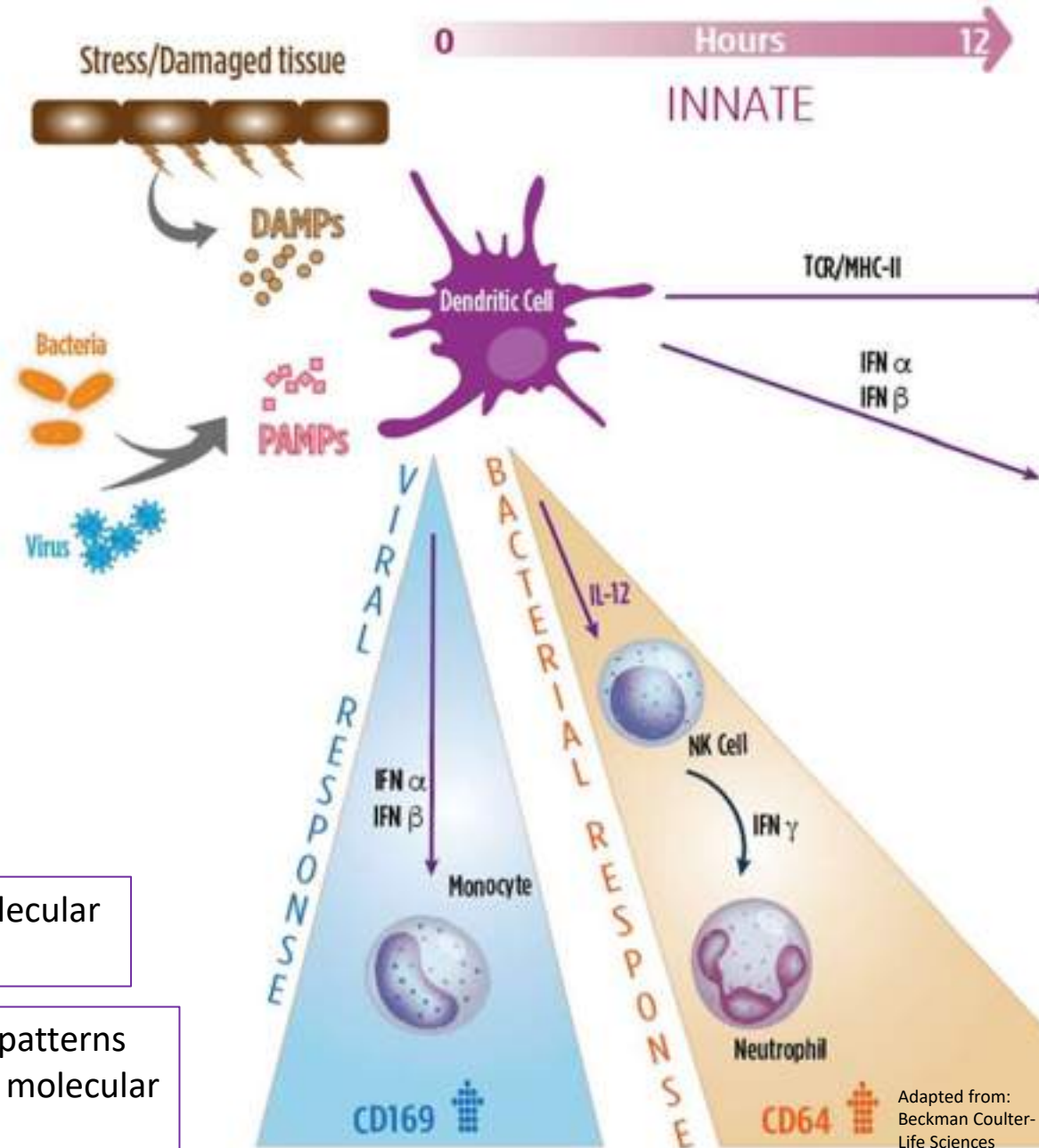
I due tipi fondamentali di immunità sono l'immunità innata e adattativa (o acquisita). Alcuni dei nostri globuli bianchi svolgono un ruolo nell'immunità innata, altri nell'immunità acquisita, mentre alcuni sono coinvolti in entrambi.



Caratteristiche e funzioni delle cellule coinvolte nel Sistema Immunitario innato

Cell	Image	% in adults	Nucleus	Functions	Lifetime	Main targets
Macrophage*		Varies	Varies	- Phagocytosis - Antigen presentation to T cells	Months – years	Various
Neutrophil		40-75%	Multi-lobed	- Phagocytosis - Degranulation (discharge of contents of a cell)	6 hours – few days	- Bacteria - Fungi
Eosinophil		1-6%	Bi-lobed	- Degranulation - Release of enzymes, growth factors, cytokines	8-12 days (circulate for 4-5 hours)	- Parasites - Various allergic tissues
Basophil		< 1%	Bi- or tri-lobed	- Degranulation - Release of histamine, enzymes, cytokines	Lifetime uncertain; likely a few hours – few days	Various allergic tissues
Mast cell		Common in tissues	Central, single-lobed	- Degranulation - Release of histamine, enzymes, cytokines	Months to years	- Parasites - Various allergic tissues
Lymphocytes (T cells)		20-40%	Deeply staining, eccentric	T helper (Th) cells (CD4+): immune response mediators Cytotoxic T cells (CD8+): cell destruction	Weeks to years	- Th cells: intracellular bacteria - Cytotoxic T cells: virus infected and tumour cells - Natural killer cells: virus-infected and tumour cells
Monocyte		2-6%	Kidney shaped	Differentiate into macrophages and dendritic cells to elicit an immune response	Hours – days	Various
Natural killer (NK) cell		15% (varies) of circulating lymphocytes and tissues	Single-lobed	- Tumour rejection - Destruction of infected cells - Release of perforin and granzymes which induce apoptosis	7-10 days	- Viruses - Tumour cells

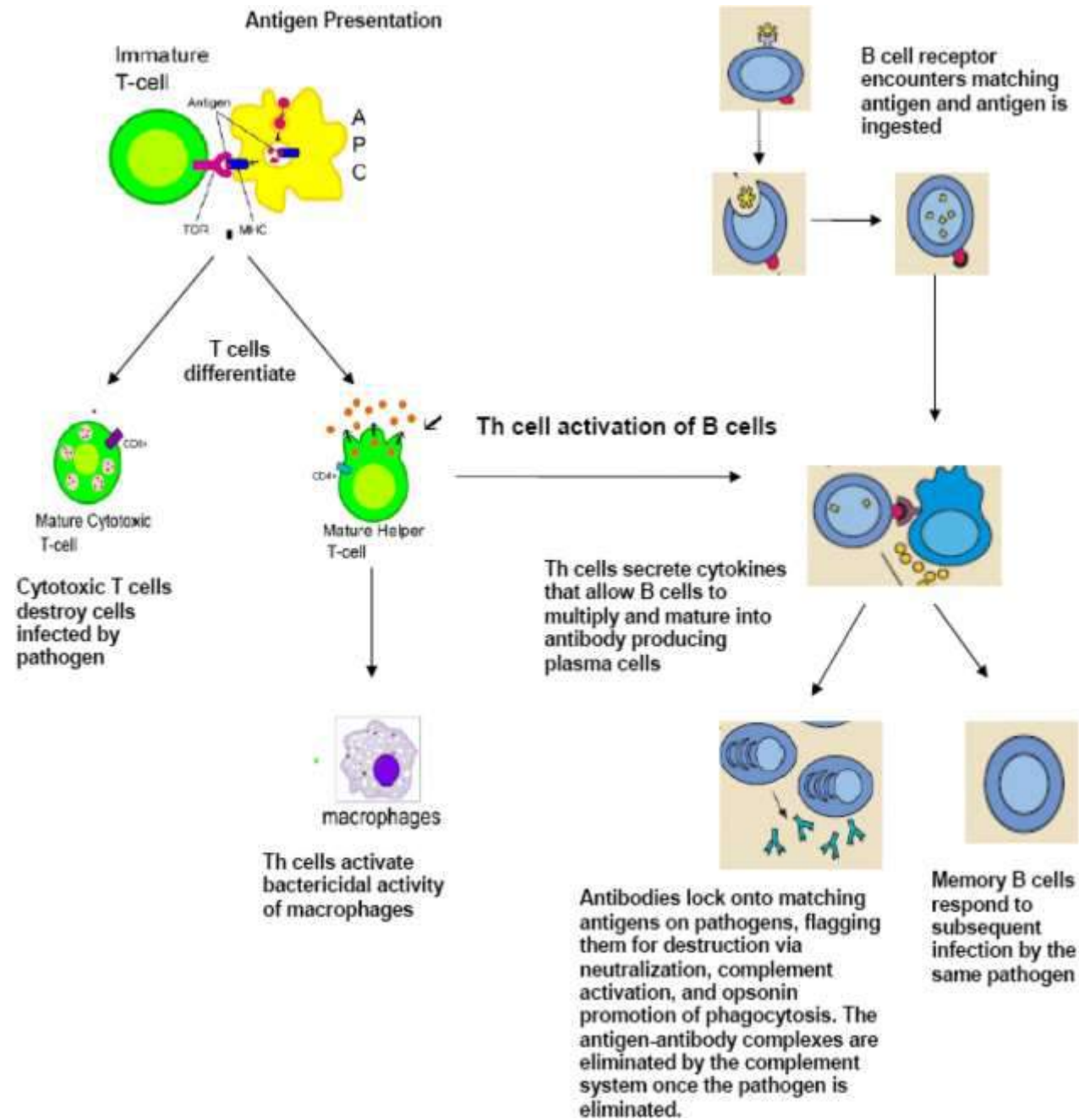
Sistema Immunitario: la Risposta Innata



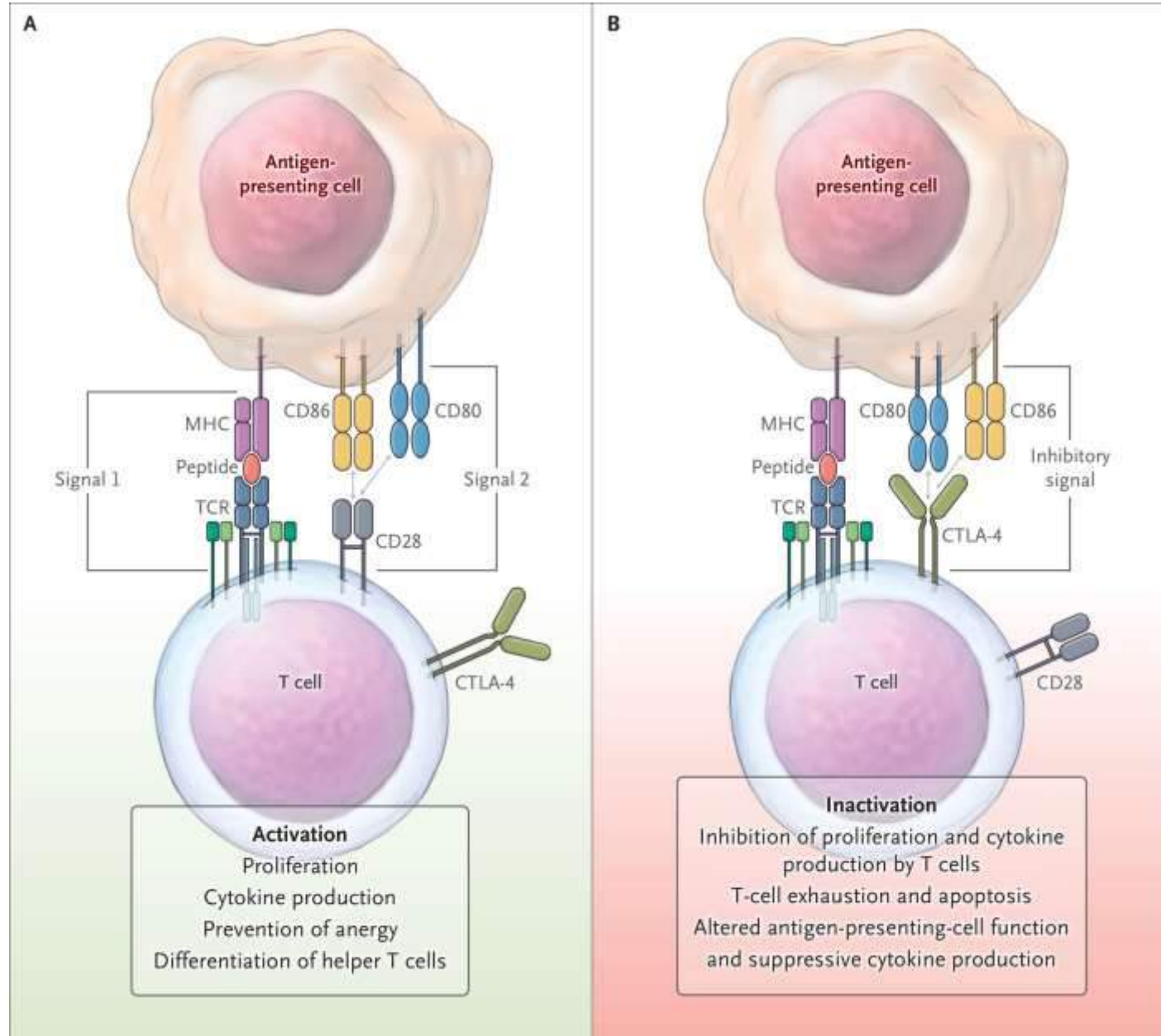
DAMPs: Damage/Danger-associated molecular patterns

PAMPs: Pathogen-associated molecular patterns
Also called **MAMPs:** Microbe-associated molecular patterns

Sistema Immunitario: la risposta adattativa

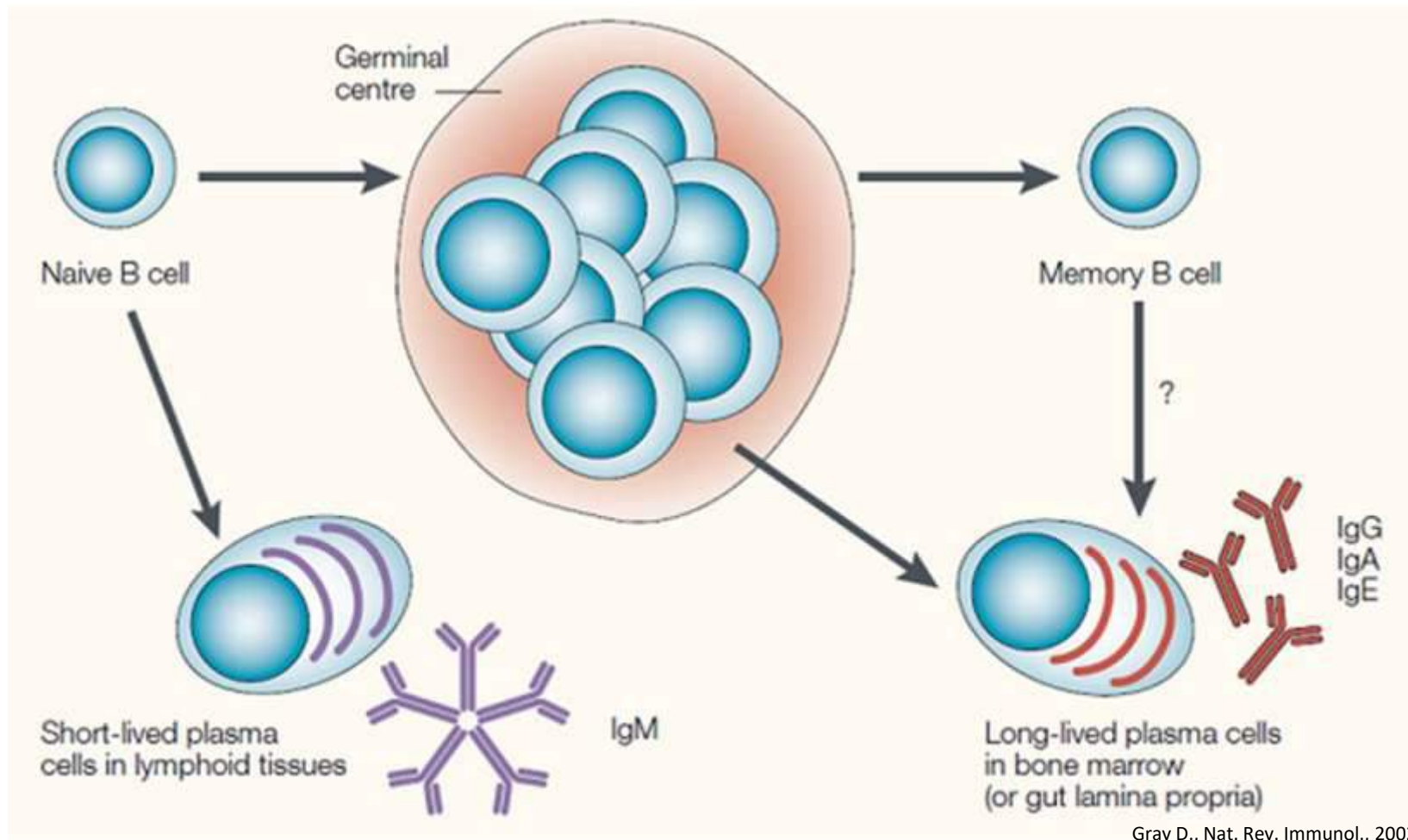


Cellule T: Modelli a due segnali di recettori costimolatori e inibitori



B Cell Activation and Isotype Switching

- B cells are activated by antigen presented by MHC and co-stimulatory (CD40-CD40L) signals from Th2 cells.
- After activation, B cells undergo rounds of mutation and selection to generate high-affinity **memory B cells and plasma cells.**
- Plasma cells are B cells that secrete their antigen-specific receptors in the form of **antibodies.**

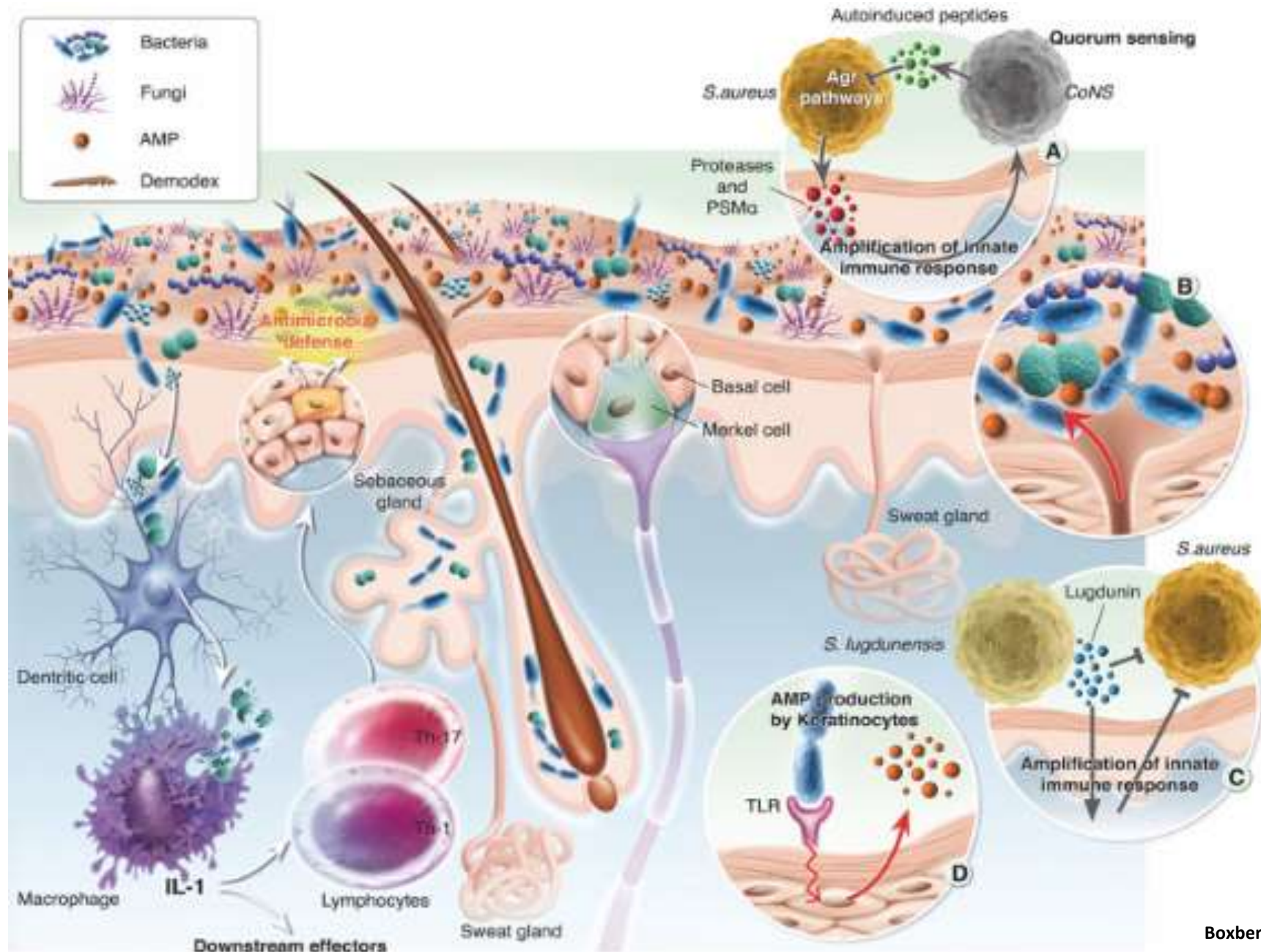


Confronto tra risposta innata ed adattativa

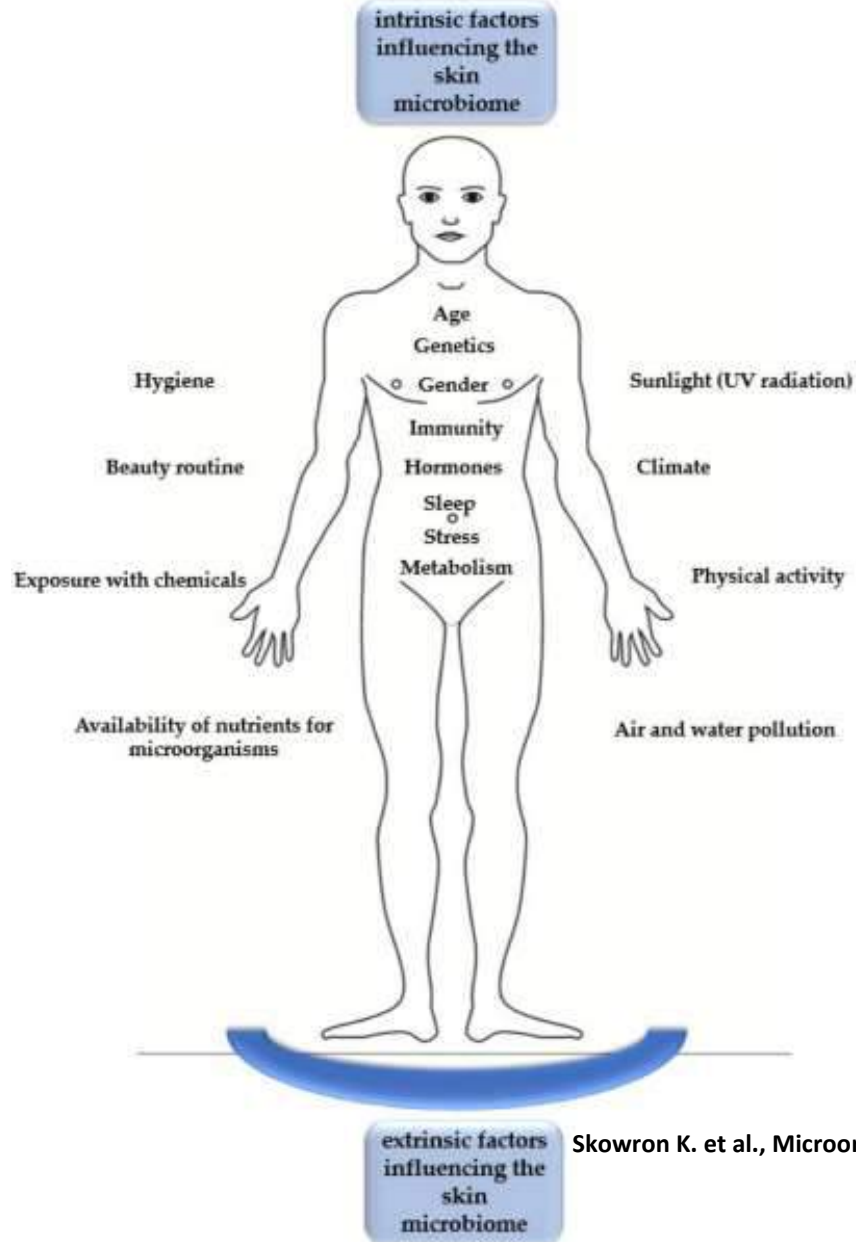
	Innate immune system	Adaptive immune system
Cells	Hematopoietic cells: • Macrophages • Dendritic cells • Mast cells • Neutrophils • Basophils • Eosinophils • NK cells • T cells Non-hematopoietic cells • Epithelial cells (skin, airways, gastrointestinal tract)	Hematopoietic cells: • T cells • B cells
Molecules	• Cytokines • Complement • Proteins and glycoprotein	• Antibodies (Ig) • Cytokines
Response time	• Immediate	• Delayed by hours to days
Immunologic memory	• None: responses are the same with each exposure	• Responsiveness enhanced by repeated antigen exposure

Sistema immunitario e microbiota della pelle

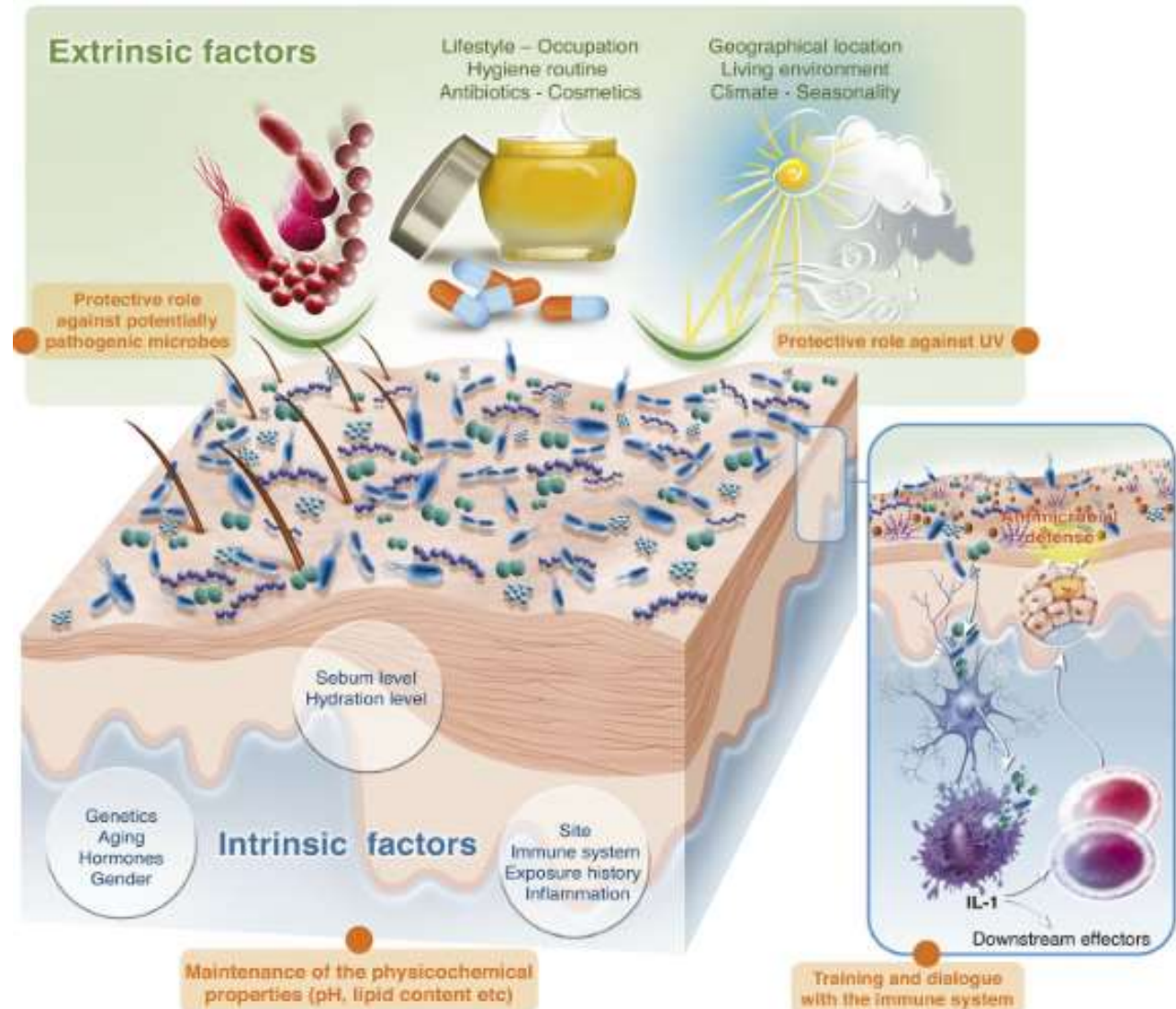
Skin microbiota, its roles, and its relationship with the immune system



The intrinsic and extrinsic factors that influence the skin microbiome



Skowron K. et al., Microorganisms, 2021

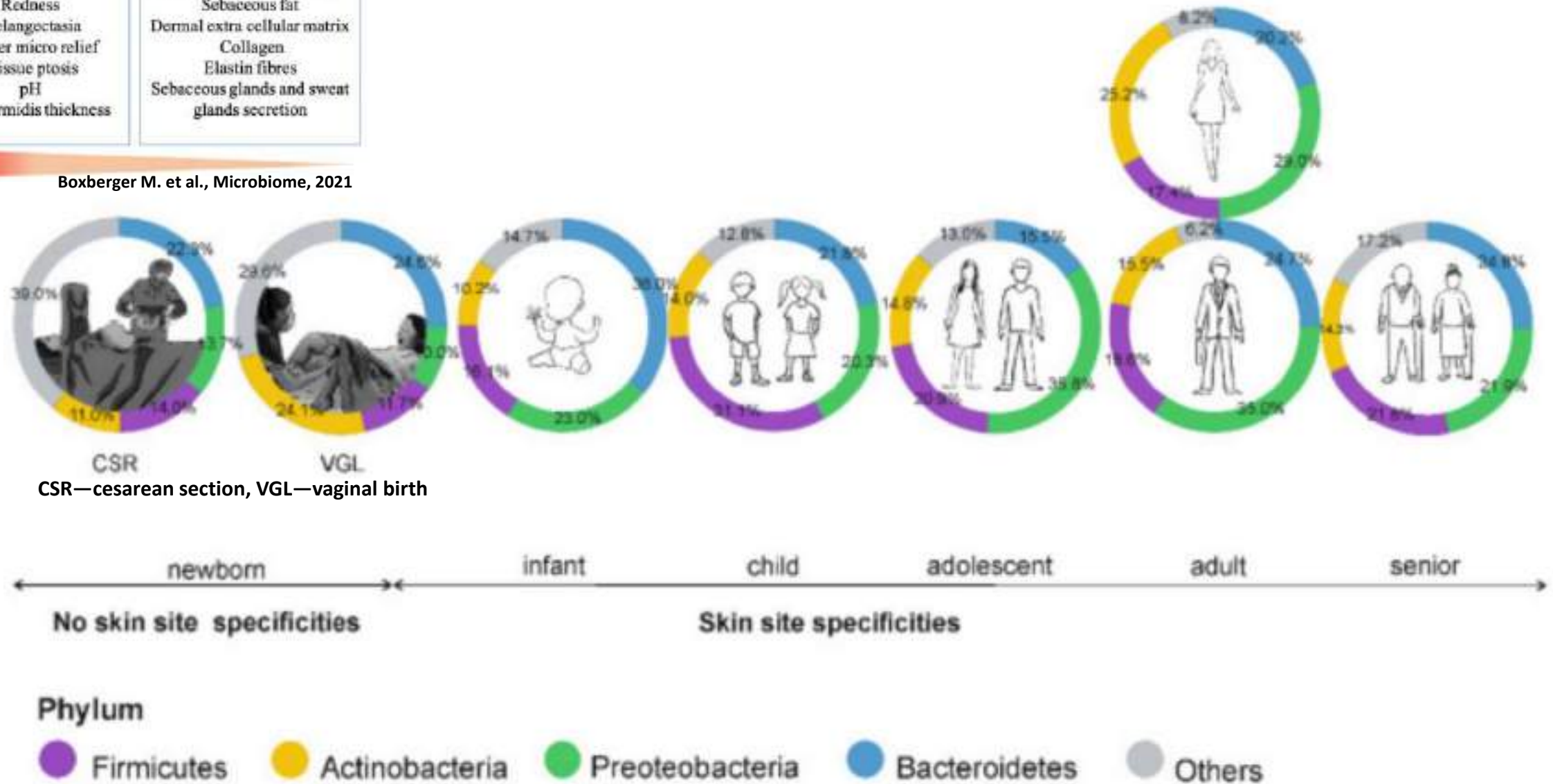


Boxberger M. et al., Microbiome, 2021

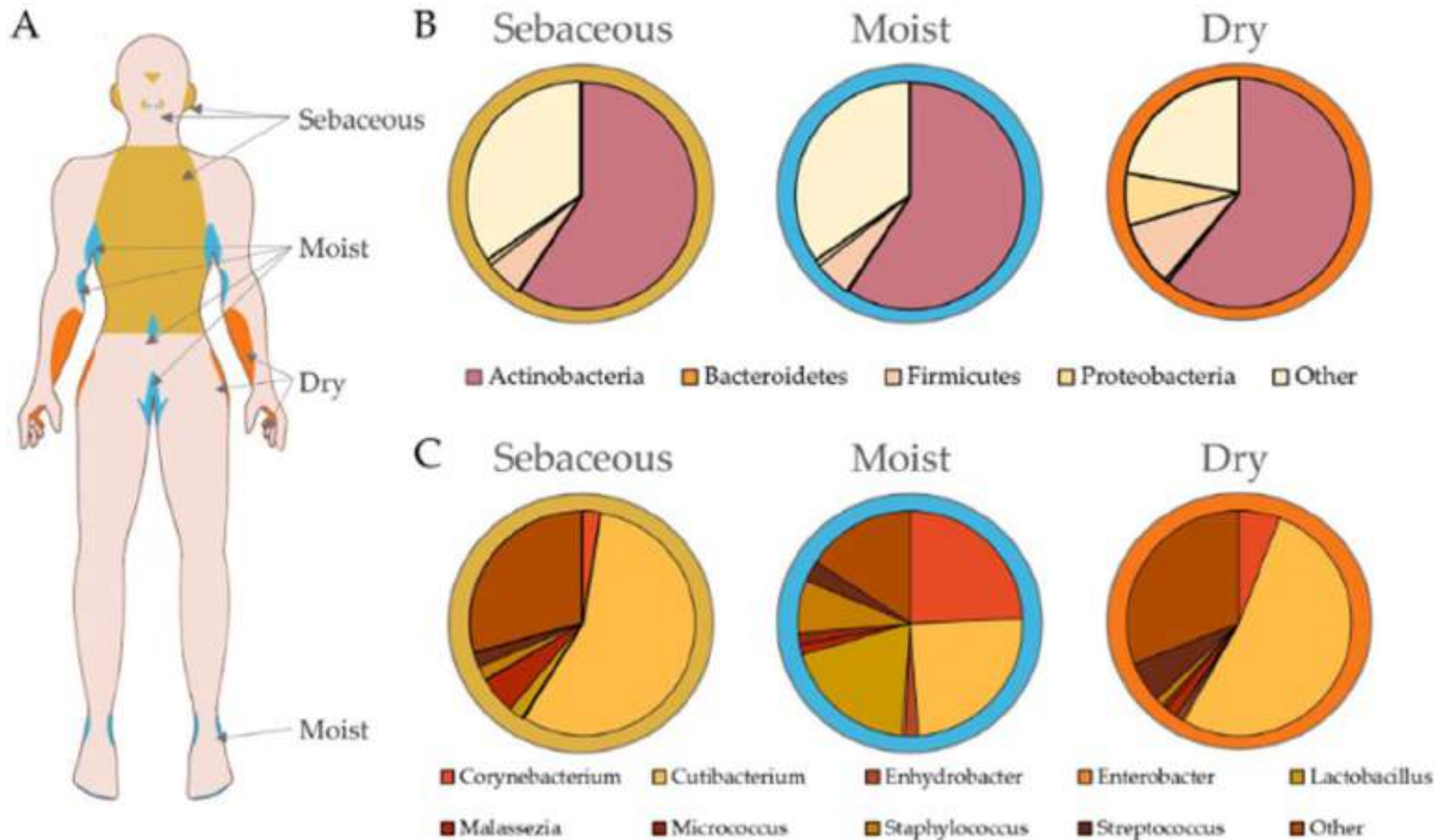
Age-dependent specificity of the skin microbiome

Increasing	Decreasing
Spots	Cell renewal
Lentigines	Pigmentation uniformity
Winkles	Sebaceous fat
Redness	Dermal extra cellular matrix
Telangiectasia	Collagen
Duller micro relief	Elastin fibres
Tissue ptosis	Sebaceous glands and sweat glands secretion
pH	
Epidermidis thickness	

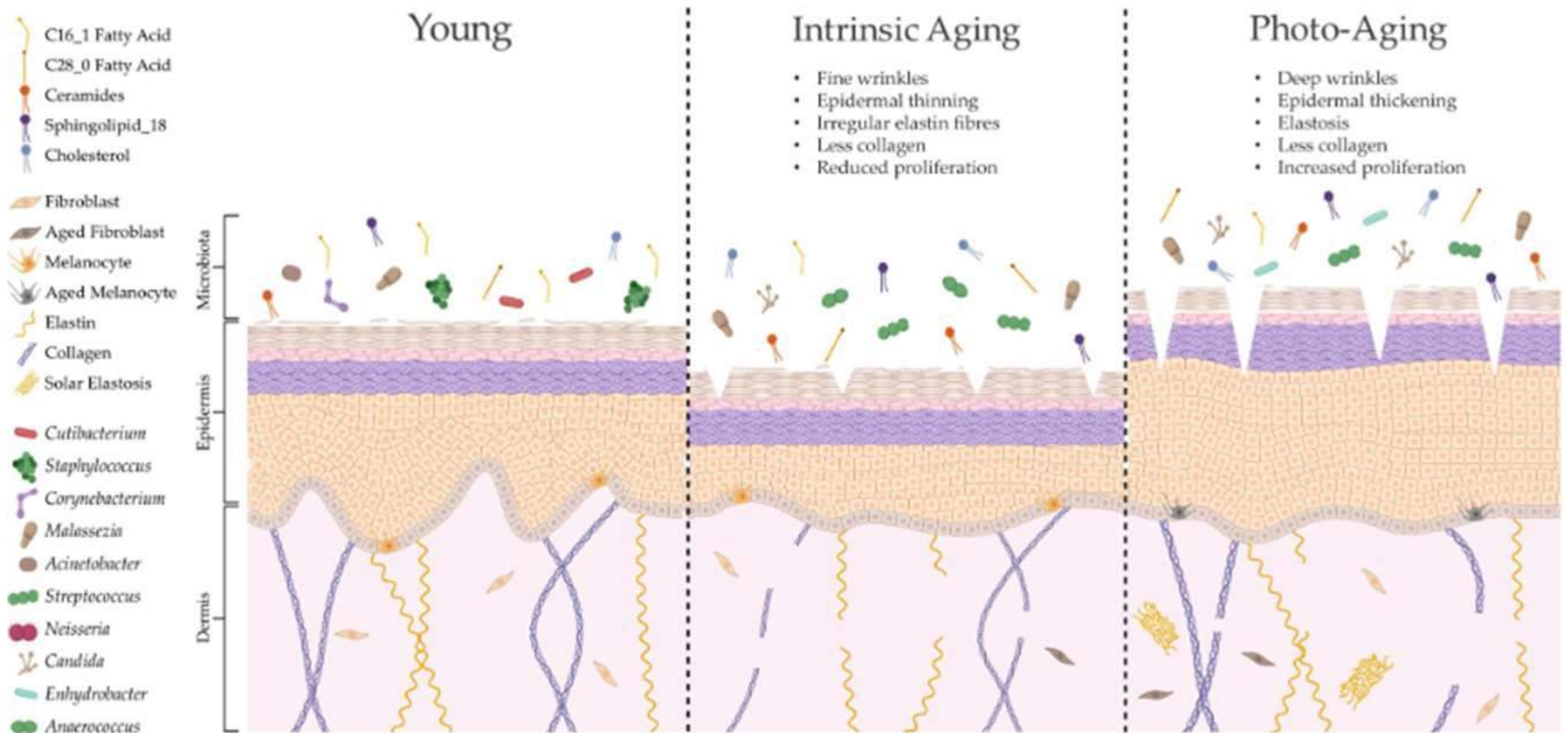
Boxberger M. et al., Microbiome, 2021



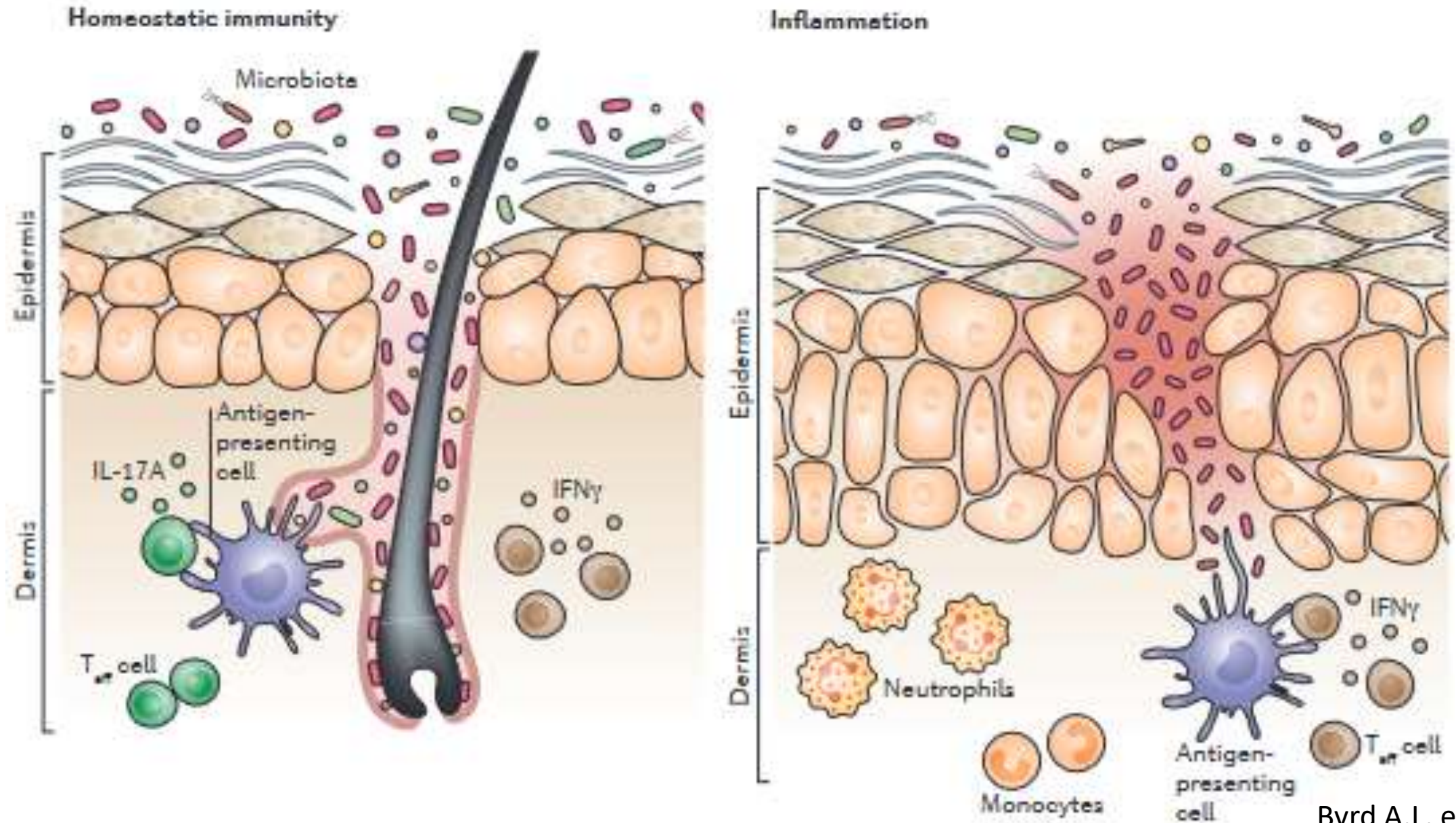
Microbial composition of the skin is dictated by topography



Ageing alters skin structure, function and microbial colonization

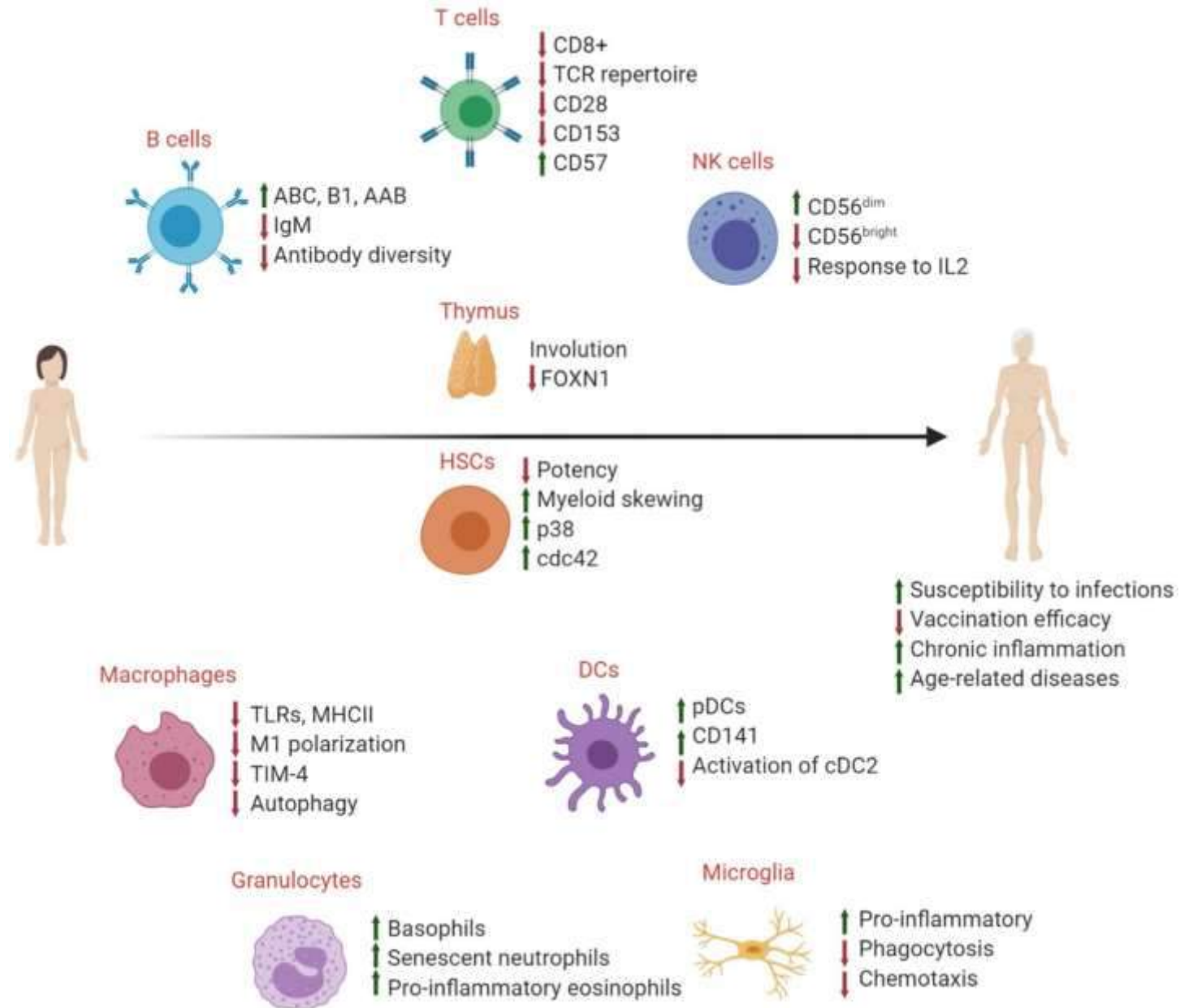


Crosstalk between the immune system and the skin microbiota

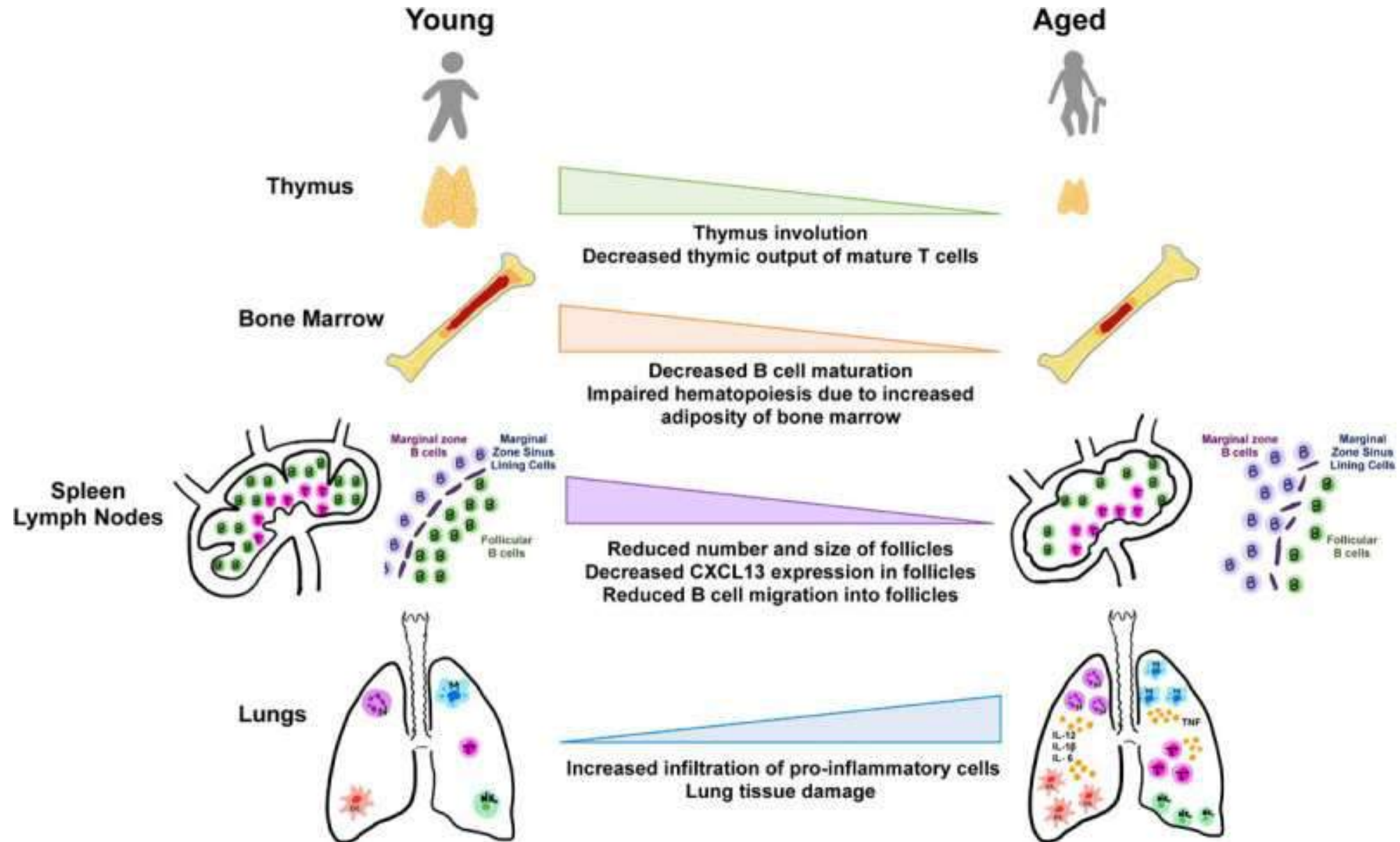


Invecchiamento e Sistema Immunitario

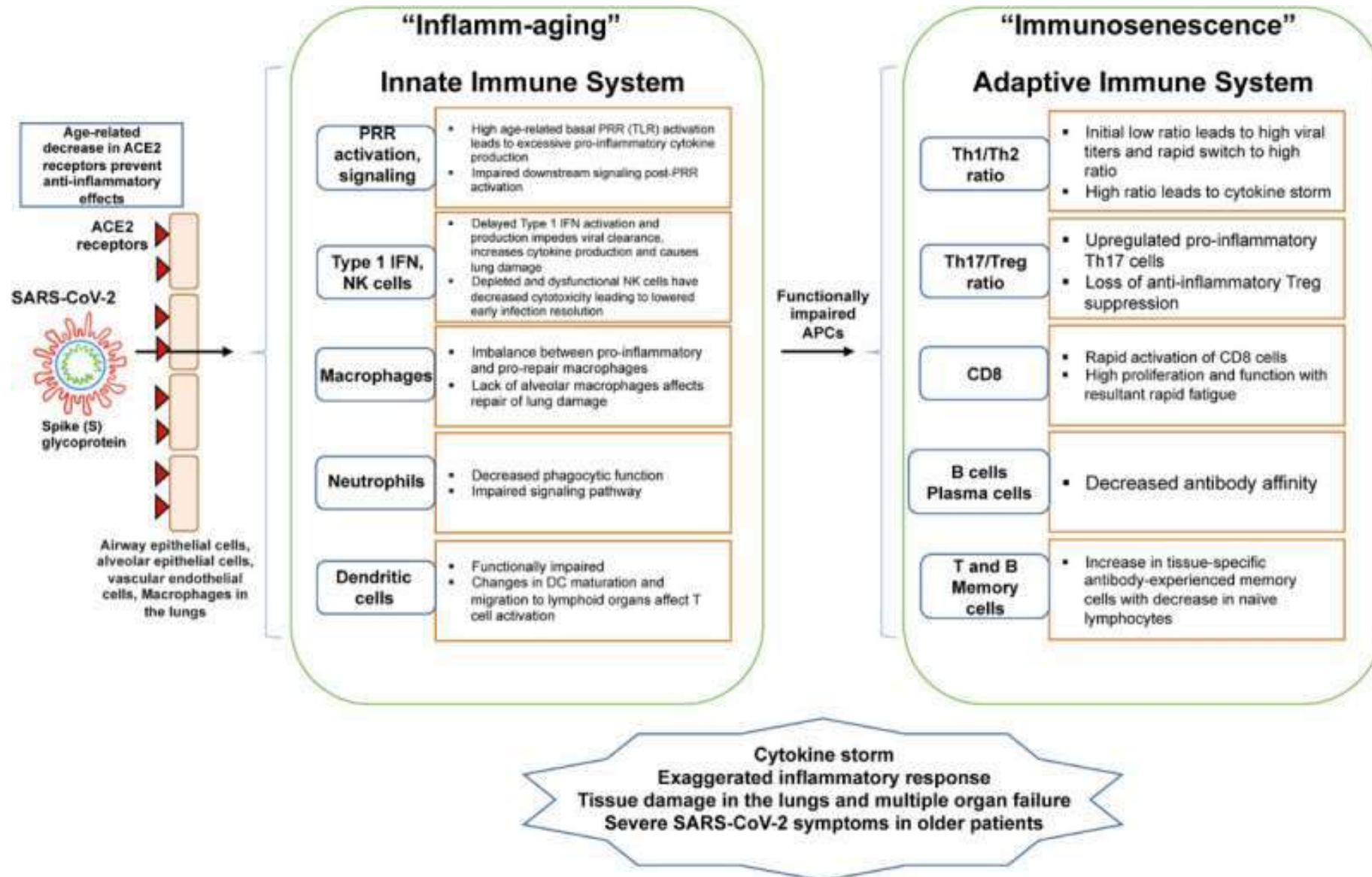
Immune alterations during ageing



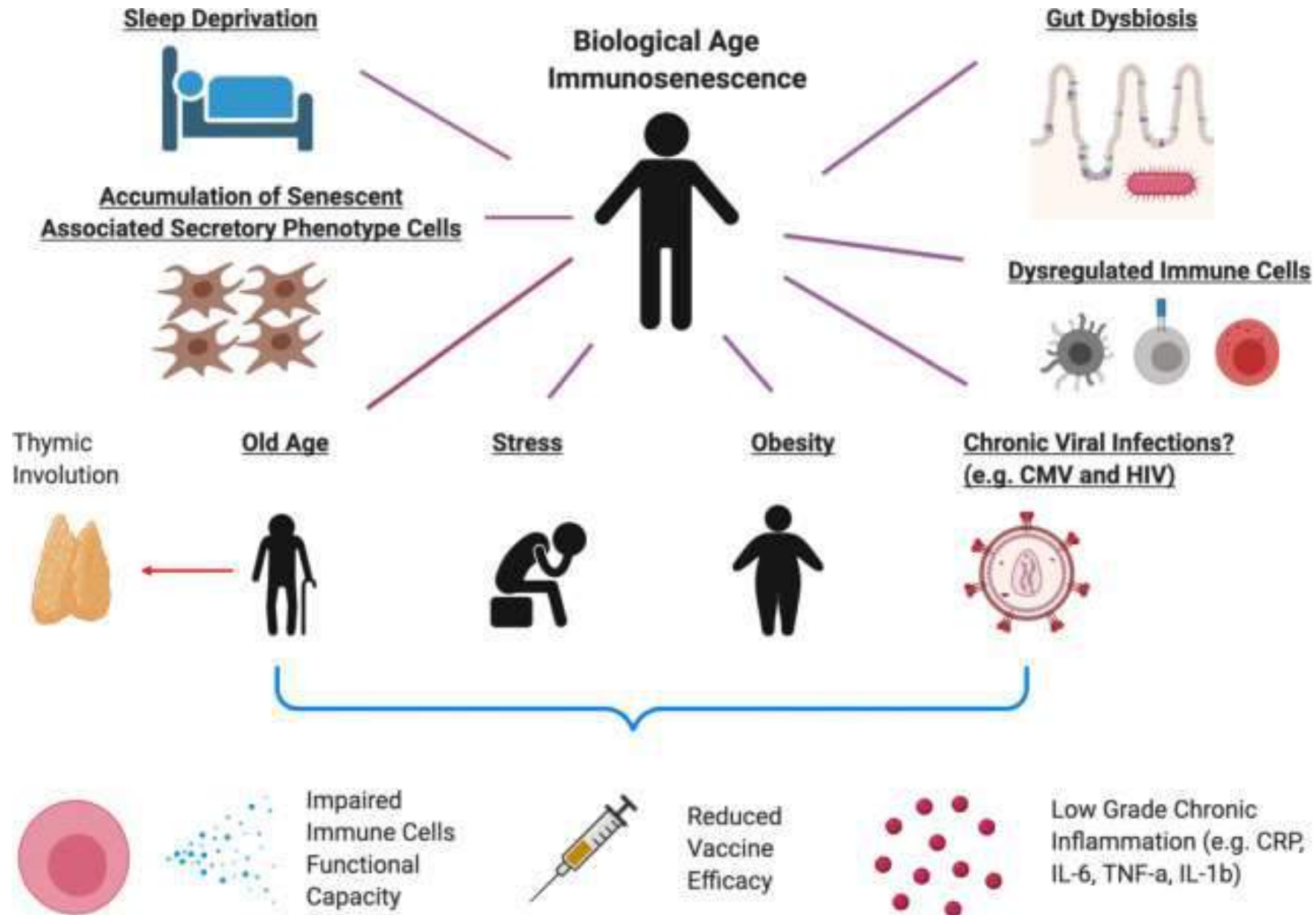
Ageing and tissues in immunity



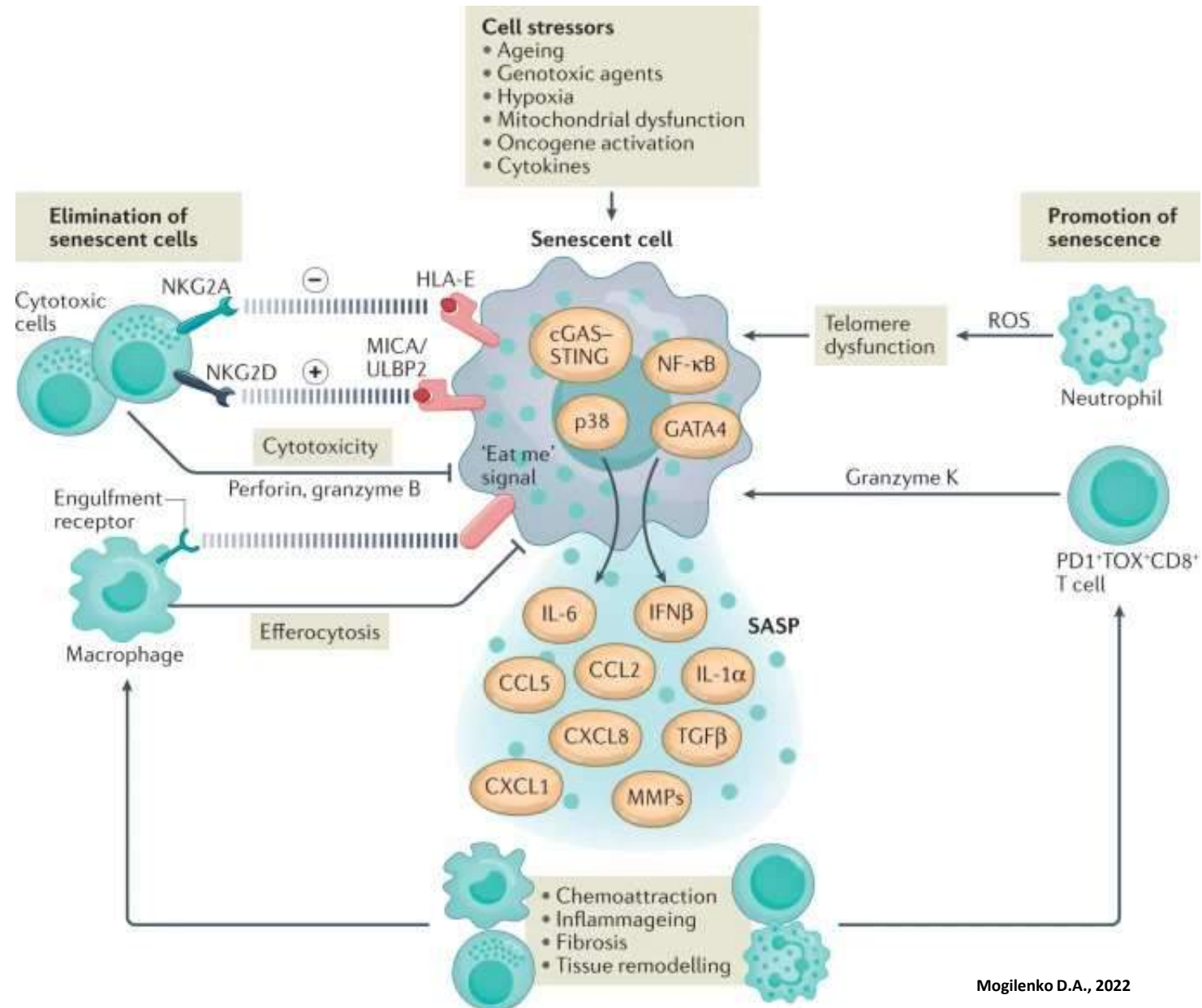
Schematic shows age-related changes in the innate and adaptive immune system with relevance to COVID-19



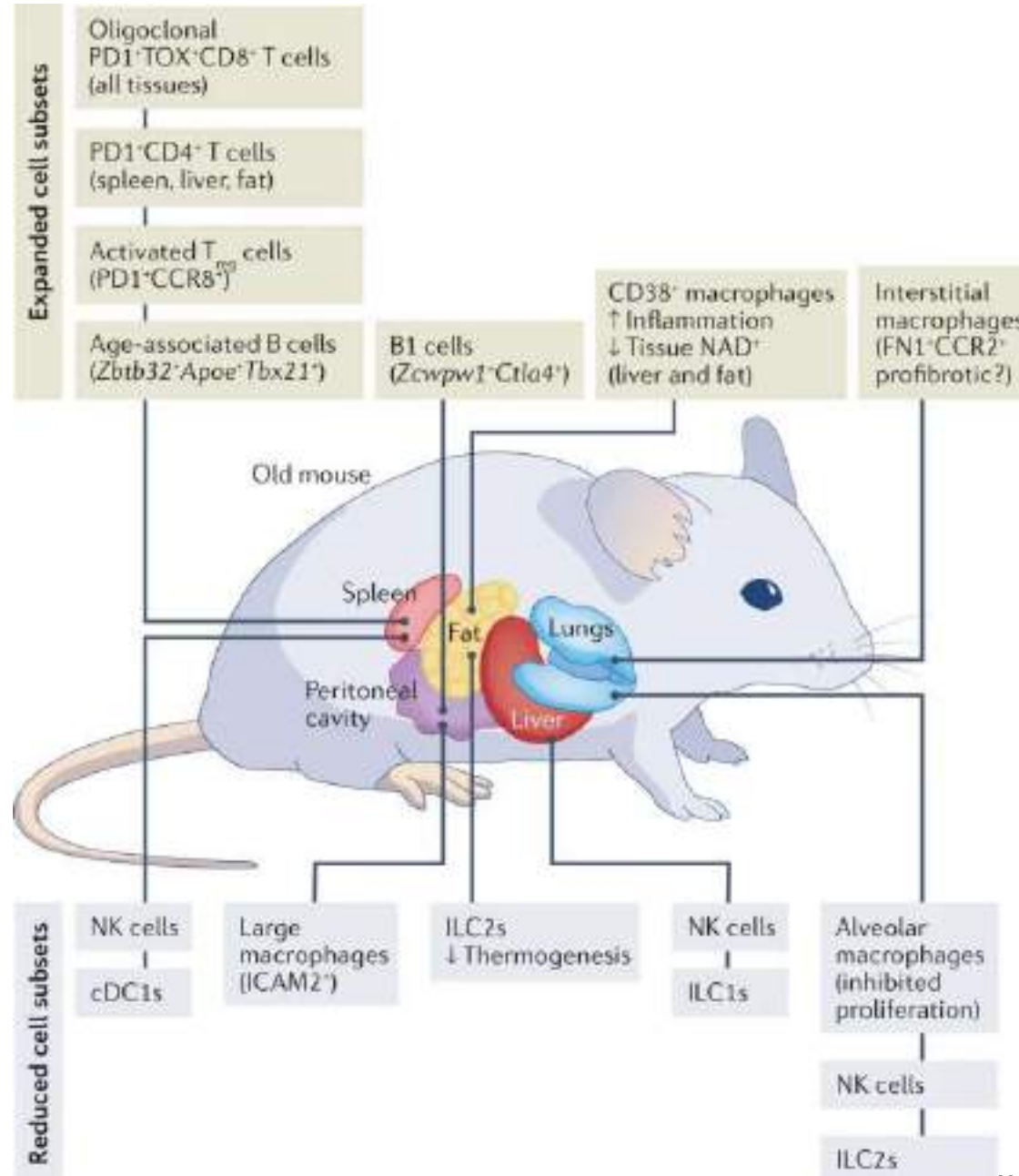
Various external stressors resulting in biological age-related immunosenescence



Interactions between immune and senescent cells

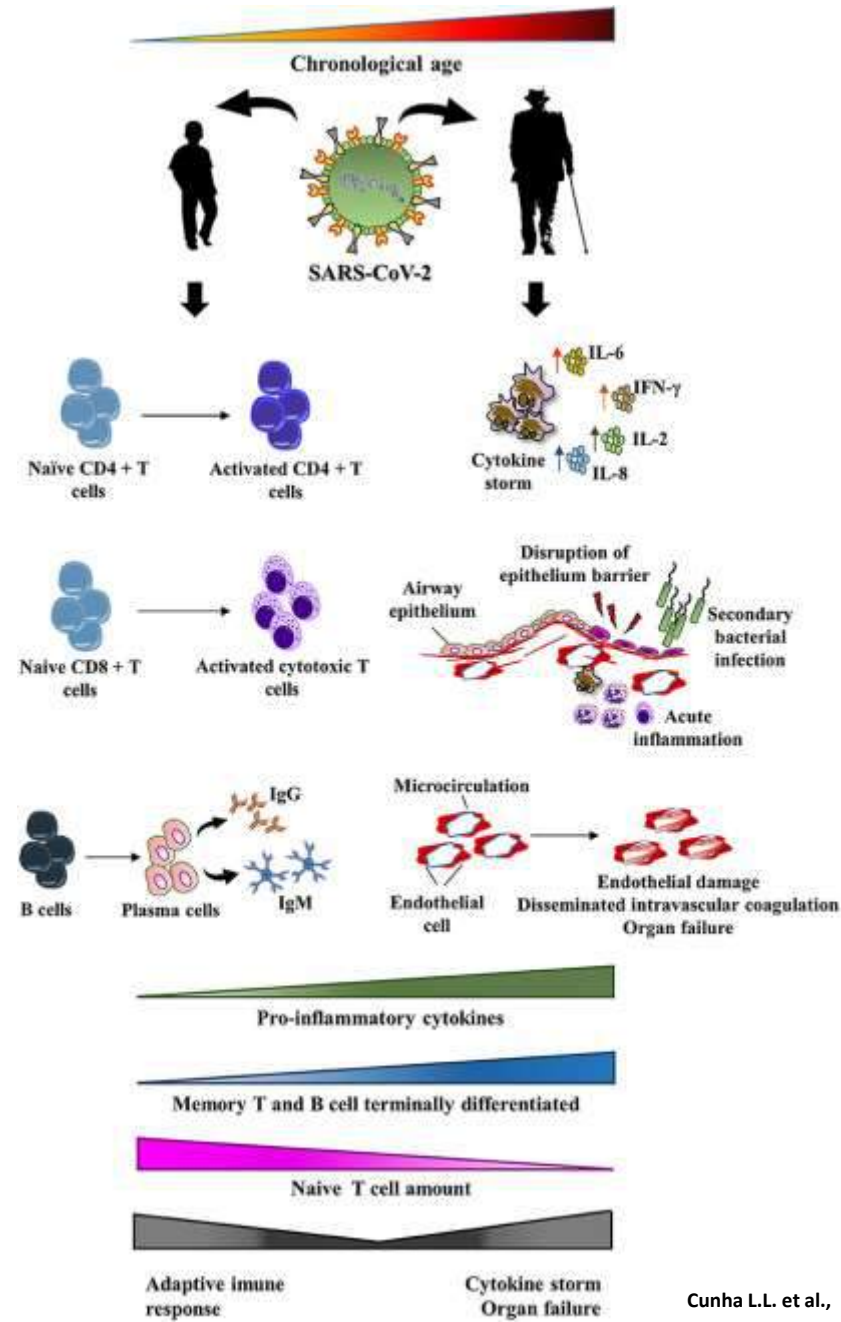


Alterations of immune cell populations in ageing



Single-cell techniques identified expanded and reduced immune cell populations with distinct phenotypes in multiple organs of old mice.

Potential impact of immunosenescence on the pathogenesis of COVID-19

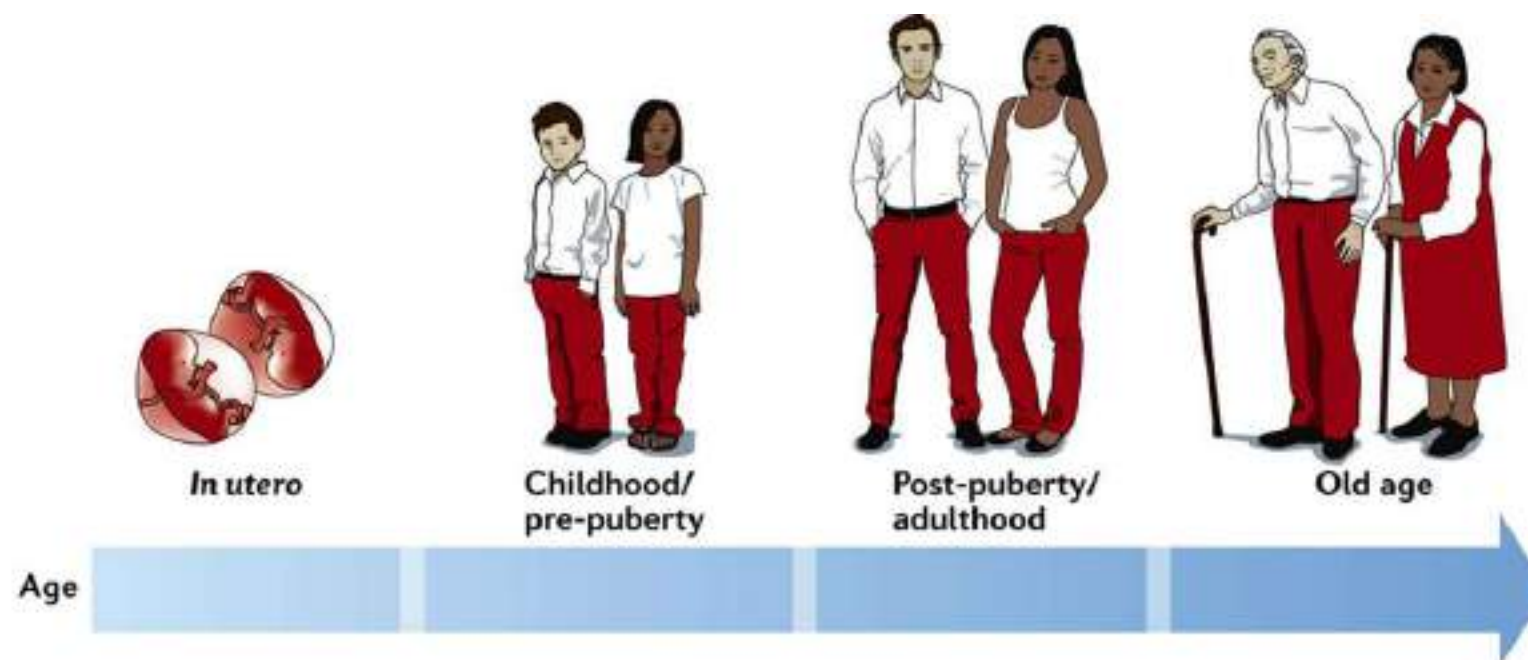


Sistema immunitario e differenze in relazione al sesso

Sex differences in immune responses in different species

Common name	Species	Immune component	Sex difference
Sea urchin	<i>Paracentrotus lividus</i>	Number of immunocytes, cytotoxic activity, phagocytosis and haemolysis	Greater in females than in males
Fruit fly	<i>Drosophila melanogaster</i>	Activation of Toll and immune deficiency signalling	Greater in females than in males
Scorpionfly	<i>Panorpa vulgaris</i>	Haemolysis and phagocytosis	Greater in females than in males
Wall lizard	<i>Podarcis muralis</i>	Macrophage phagocytosis	Greater in females than in males
Eurasian kestrels	<i>Falco tinnunculus</i>	Hypersensitivity responses	Greater in females than in males
Great tit	<i>Parus major</i>	Hypersensitivity responses	Greater in females than in males
House mouse	<i>Mus musculus</i>	Pro-inflammatory cytokine responses, T cell proliferation and antibody responses	Greater in females than in males
Rhesus macaque	<i>Macaca mulatta</i>	Pro-inflammatory cytokine responses and antibody responses	Greater in females than in males
Human	<i>Homo sapiens</i>	Type I interferon activity, T cell numbers and antibody responses	Greater in females than in males

Changes in immune responses in human males and females over the life course



Innate immunity	• Increased inflammatory responses in males	• ↑ Inflammation in males • ↑ NK cells in males	• ↑ Inflammation in females • ↑ NK cells in males	• ↑ Inflammation in males • ↑ IL-10 in females • ↑ NK cells in females
Adaptive immunity	• Increased IgE levels in males	• CD4/CD8 ratios and CD4⁺ T cell numbers equal • CD8⁺ T cell numbers equal • IgA levels in males ≥ females • IgM levels in males ≥ females • IgG and IgM levels equal • B cell numbers equal • T_{reg} cell numbers in males ≥ females	• CD4/CD8 ratios and CD4⁺ T cells ↑ in females • CD8⁺ T cells ↑ in males • T cell activation/proliferation ↑ in females • T_{reg} cells ↑ in males • B cells ↑ in females • Immunoglobulins ↑ in females	• CD4/CD8 ratios and CD4⁺ T cells ↑ in females • CD8⁺ T cells ↑ in males • T cell activation/proliferation ↑ in females • T_{reg} cells ↑ in males • B cells ↑ in females • Immunoglobulins ↑ in females

Sex differences in innate and adaptive immune responses in young and aged individuals

	 Dendritic cells	 Monocytes and macrophages	 Granulocytes	 Innate lymphoid cells	 Natural killer cells	 B cells	 T cells
Young adults	♀ > ♂ TLR7 activity (H) Type 1 IFN activity (H)	♀ > ♂ Activation (M) Phagocytic capacity (M) IL-10 production (M) M2 polarization (M)	♀ > ♂ Phagocytic capacity (M) Neutrophil count (M) Nitric Oxide production post stimulation (H, R, M)	♀ > ♂ Type 2 cytokine levels upon stimulation (M)		♀ > ♂ B cell numbers (H, M) Antibody production (H, M) % switched memory B cells (H)	♀ > ♂ CD4 ⁺ T cell count (H, M) CD4 ⁺ /CD8 ⁺ T cell ratio (H) Activated T cell count (M) T cell proliferative capacity (M) Cytotoxic T cell activity (H)
	♂ > ♀ IL-10 production (R, H)	♂ > ♀ TLR4 expression (M) Pro-inflammatory cytokine production (M) M1 polarization (M)	♂ > ♀ Neutrophil attractant chemokines (R) TLR9 expression (M)	♂ > ♀ Type 2 ILC count (H) IL-13 production upon stimulation (M)	♂ > ♀ NK cell activity (R) ♀ = ♂ NK cell count (H)		♂ > ♀ CD8 ⁺ T cell count (M) T _{reg} count (M)
Aged adults	♀ > ♂ Nitric oxide synthesis (H) Mammalian family of mitogen-activated protein kinases (MAPK) signaling (H, M)	♀ > ♂ CD62L, CD115 (H) expression			♀ > ♂ NK cytotoxicity (H) Immunosurveillance (H)	♀ > ♂ Antibody production (H) Age-associated B cell count (H, M)	♀ > ♂ CD3 ⁺ T cell count (H) CD4 ⁺ T cell count (P) CD4 ⁺ /CD8 ⁺ T cell ratio (P) T _H 1 response (M)
	IL-15 production (H)		ND	ND			T _H 1 response (M) Naïve CD8 ⁺ T effector memory cells (p) T cell proliferative capacity (H, P) ♂ > ♀ CD8 ⁺ T cell count (P)

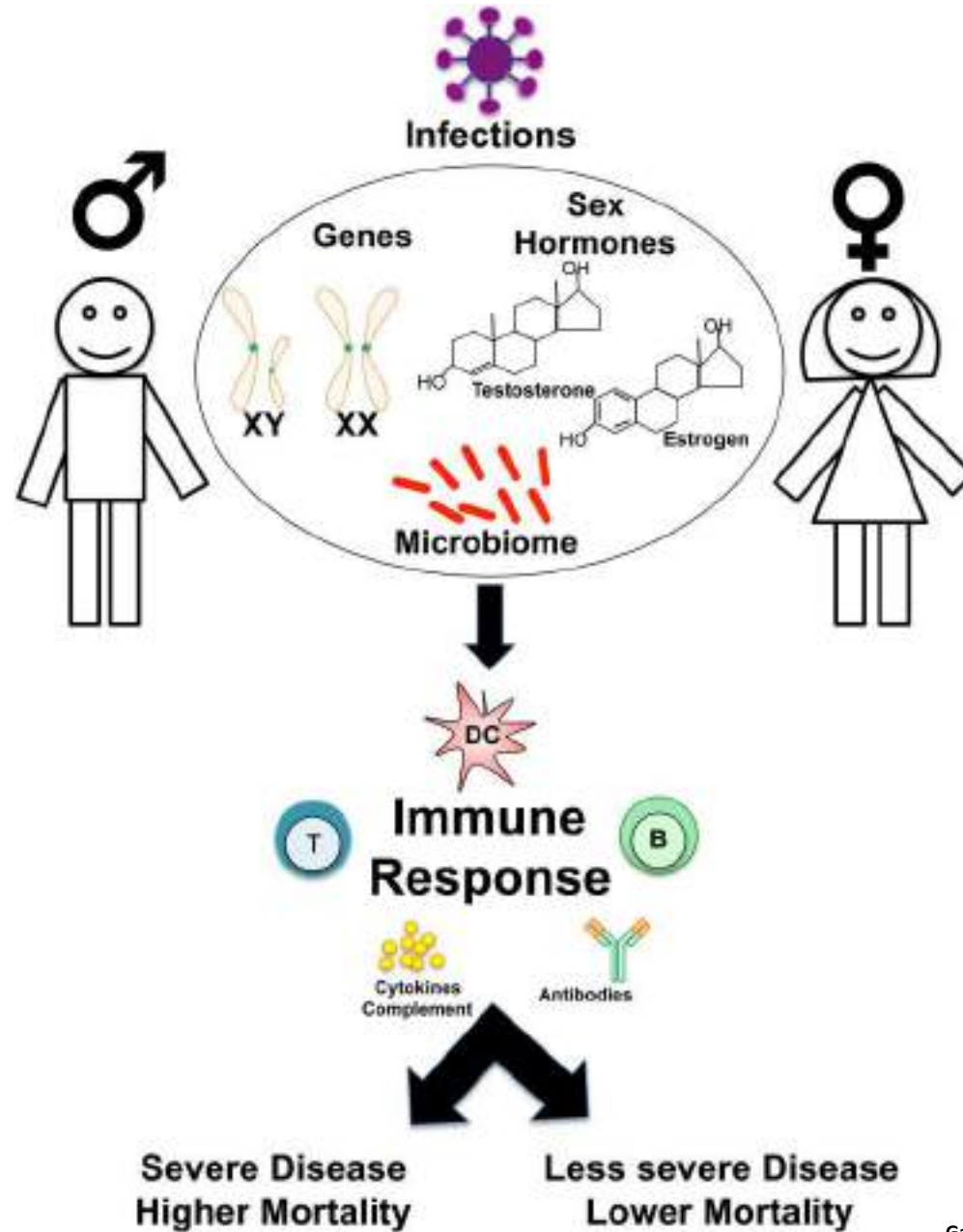
Data are from studies of mice (M), rats (R), non-human primates (P), and humans (H) (125–131).

ND, not determined.

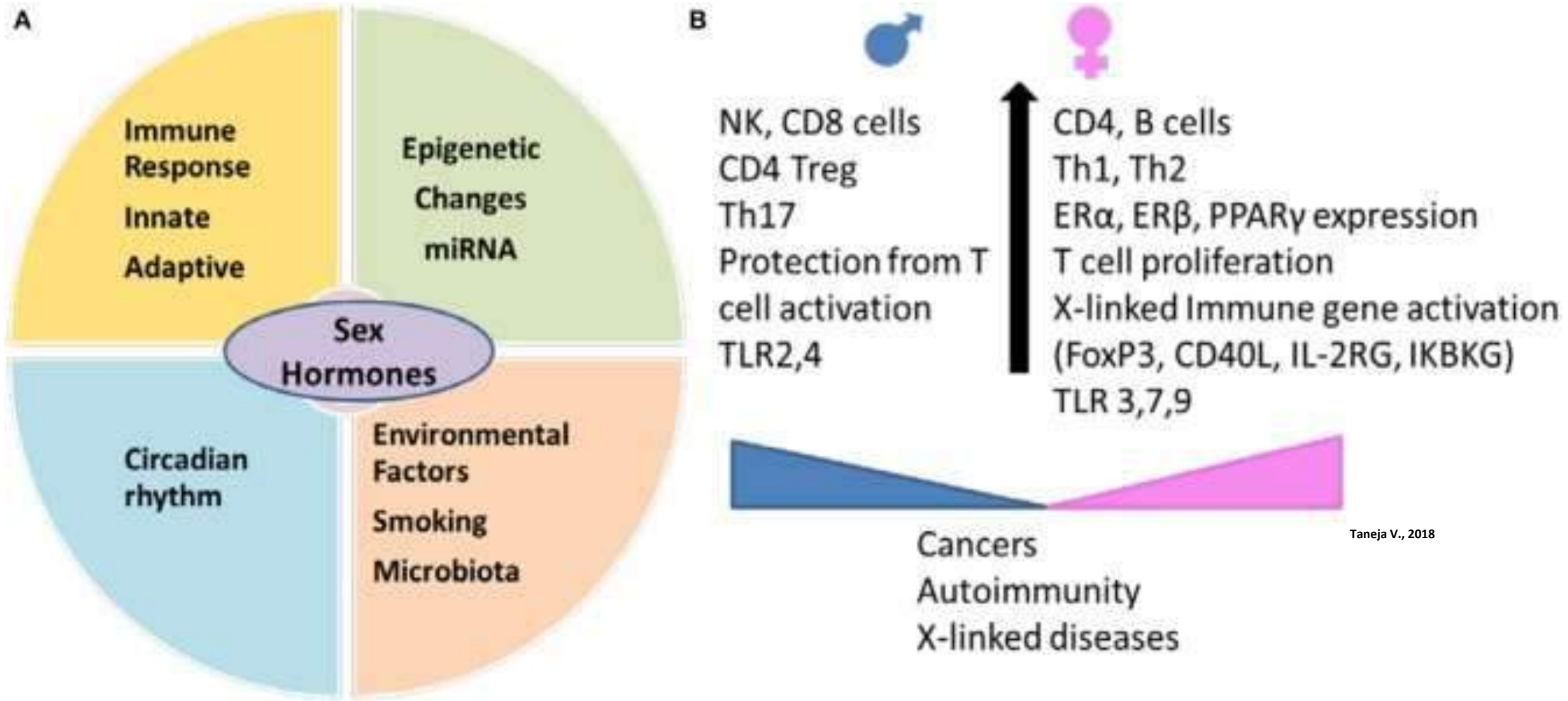
I piu' studiati ormoni sessuali

- Il **progesterone** è un ormone naturale importante per la regolazione dell'ovulazione e delle mestruazioni, prodotto in quantità elevate dalle ovaie. È anche prodotto in quantità minori dalle ghiandole surrenali sia maschili che femminili. Il progesterone ha un effetto principalmente antinfiammatorio.
- Il **testosterone** viene secreto principalmente dai testicoli maschili ed in misura minore dalle ovaie femminili. Il testosterone è il principale ormone androgeno in quanto svolge un ruolo chiave nello sviluppo dei tessuti riproduttivi maschili come i testicoli e la prostata. Promuove inoltre le caratteristiche sessuali secondarie come l'aumento della massa muscolare e ossea e la crescita dei peli corporei. In entrambi i sessi il testosterone è coinvolto nella salute e nel benessere: influenza infatti gli stati d'animo, il comportamento ed è coinvolto nella prevenzione dell'osteoporosi.
- **Gli estrogeni** sono un gruppo di ormoni che svolgono un ruolo importante nel normale sviluppo sessuale e riproduttivo nelle donne. Anche nei maschi gli estrogeni hanno ruoli fisiologici importanti, nonostante i livelli siano significativamente più bassi rispetto alle femmine. Gli estrogeni hanno un effetto bifasico: evidenziate in gravidanza o nella fase follicolare del ciclo mestruale, hanno un ruolo prevalentemente antinfiammatorio, mentre le basse concentrazioni che si osservano nelle rimanenti fasi del ciclo mestruale hanno effetti opposti.
- **la prolattina** ha una duplice funzione, sia di ormone che di citochina, e agisce sul sistema immunitario stimolando principalmente la secrezione di IL-6 e INF- γ . Altri effetti indotti dalla prolattina sono un'aumentata produzione di anticorpi e sviluppo di cellule presentanti l'antigene. L'iperprolattinemia sia stata descritta in relazione alla patogenesi di diverse malattie autoimmuni [30], e di seguito menzioneremo brevemente a titolo di esempio il **Lupus Eritematoso Sistemico**, l'**artrite reumatoide** e la **sclerosi multipla**, la **celiachia** e la **malattia tiroidea autoimmune**.

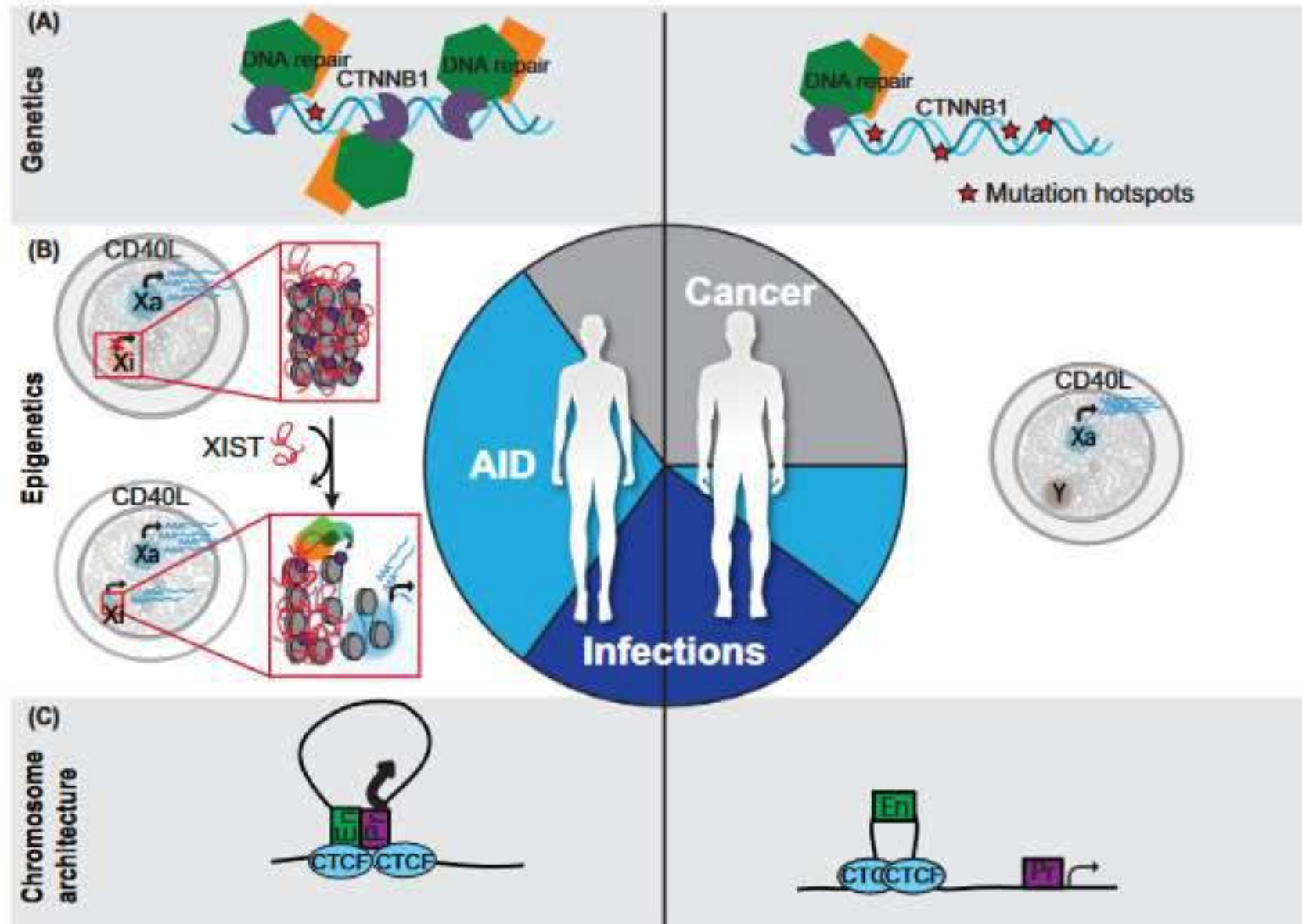
Overview of sex-based differences in the immune response to Infections



Sex hormones interact with genetic and environmental factors and determine immunity in an individual

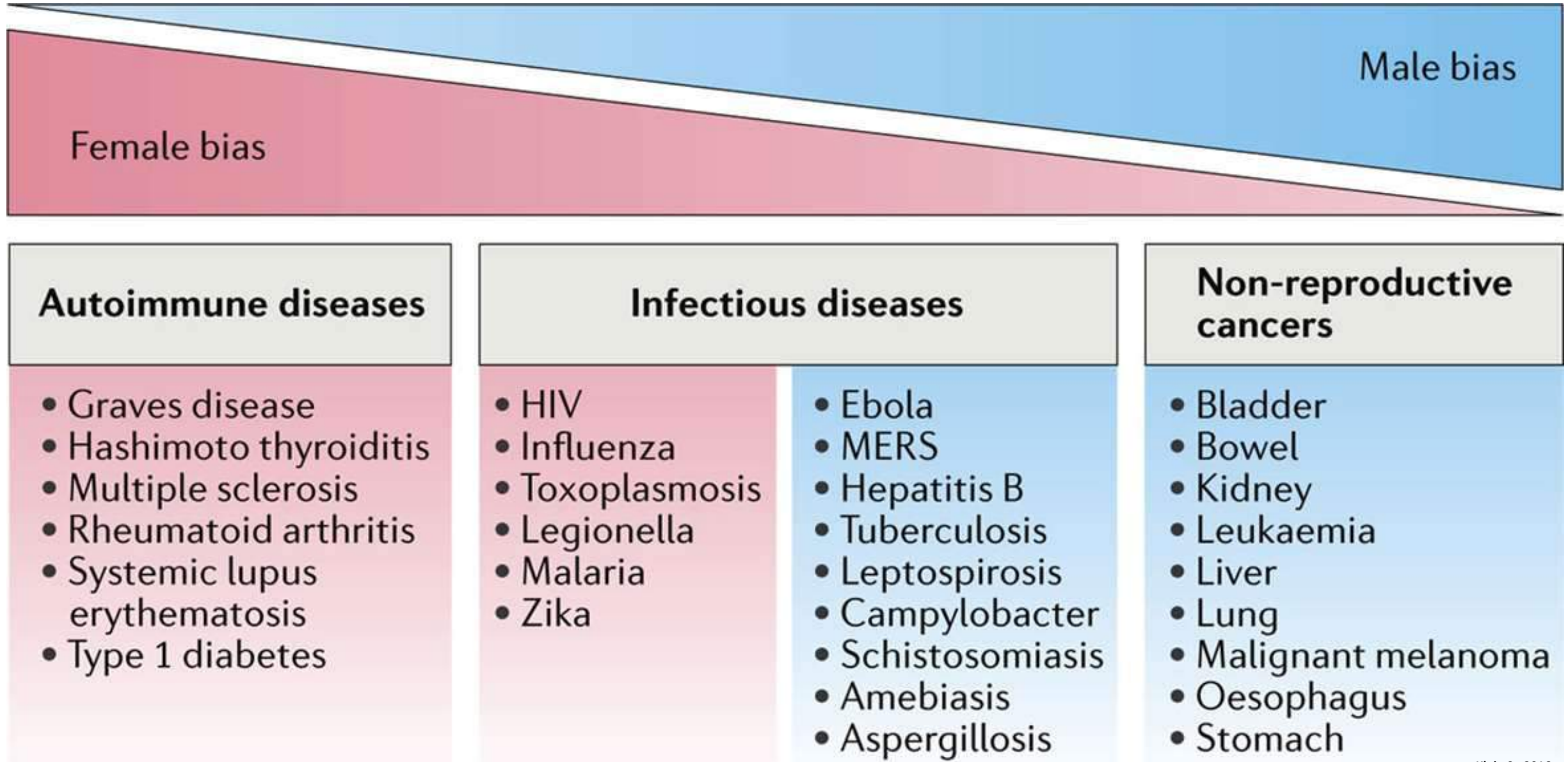


Differences in Mutational Processes, Epigenetic States, and Chromosome Architecture Underlie Sex Bias in Human Disease

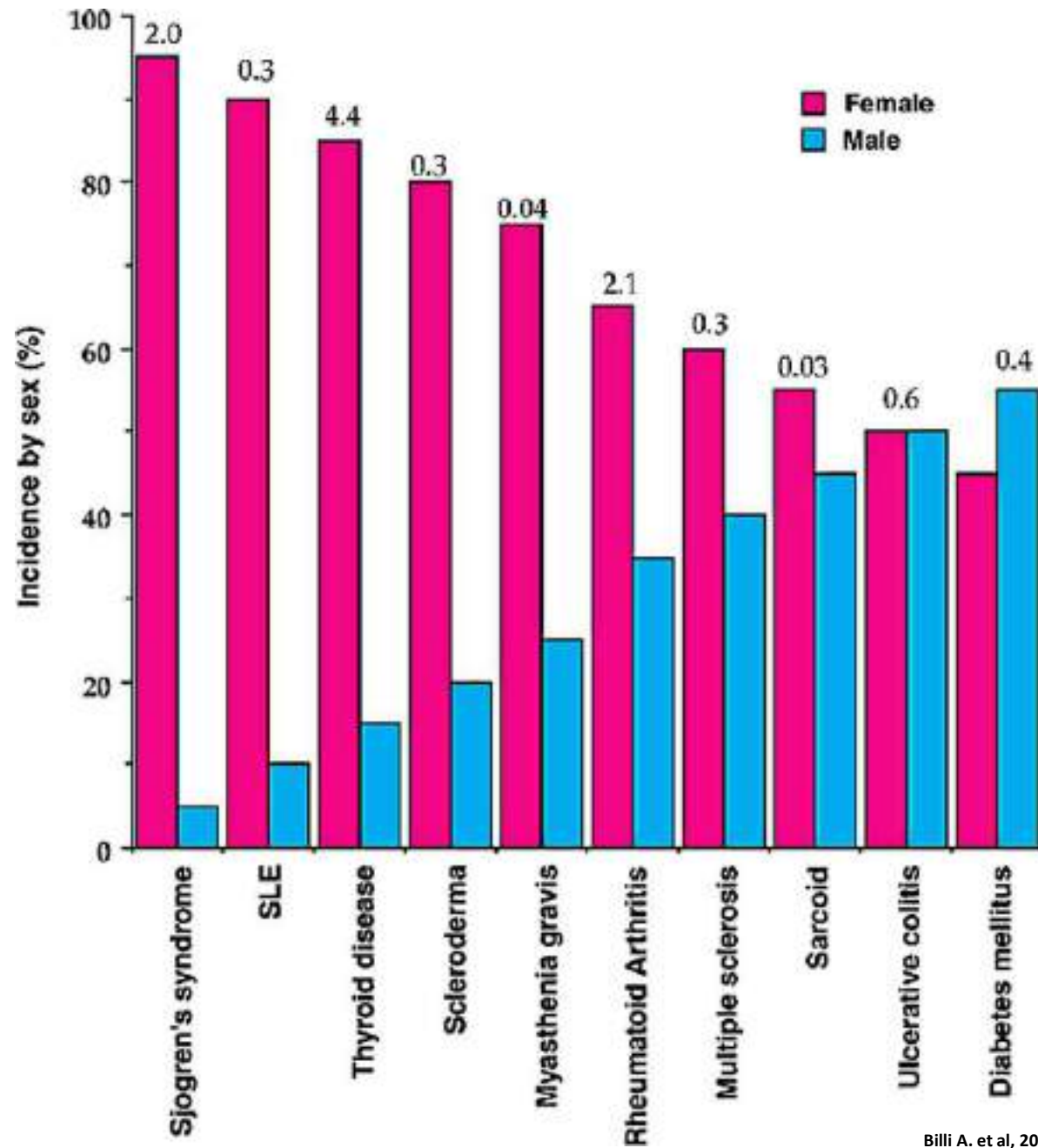


AID: Auto-immune diseases

Sex-related bias in autoimmune diseases, infectious diseases and cancers



The sex distribution of the major autoimmune diseases

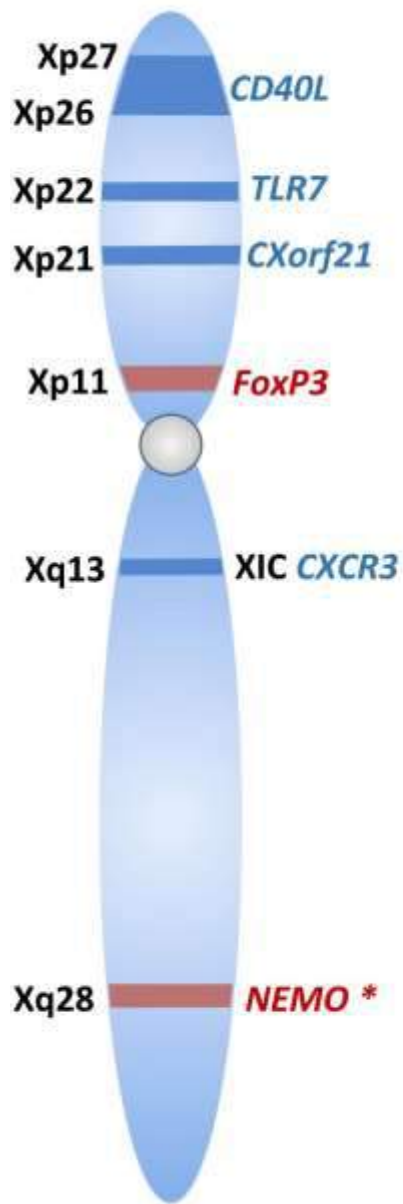


Sex differences in responses to vaccines

Target group	Vaccine	Sex difference in Immune response	Sex difference in adverse reactions	Age (years)
Children	Hepatitis B	Greater in females	Not defined	<12
	Diphtheria	Greater in females	Not defined	<2
	Pertussis	Greater in females	Not defined	<2
	Pneumococcal	Greater in females	Not defined	6–9
	Rabies	Greater in females	Not defined	6–9
	Measles	Greater in females or equivalent in both sexes	Increased in females	<3
	RTS,S vaccine against malaria	Greater in females	Increased in females	<2
	Human papillomavirus	Greater in females	Increased in females	5–17
Adults	Influenza	Greater in females	Increased in females	18–49
	Hepatitis B	Greater in females	Increased in females	>18
	Herpes virus	Greater in females	Not defined	>18
	Yellow fever	Greater in females	Increased in females	>18
	Rabies	Greater in females	Not defined	>18
	Smallpox	Greater in females	Not defined	>18
Aged adults	Influenza	Greater in females	Increased in females	>65
	Td/Tdap	Greater in males	Increased in females	>65
	Pneumococcal	Greater in males	Increased in females	>65
	Shingles	Not defined	Increased in females	>65

Immune-related Genes implicated in the sex-based differences in the immune response

X Chromosome



Chromosome 6



Chromosome	Gene	XCI Escape	Primary Immune Effect	Mechanism
X				CD4+ T cell proliferation
	CD40L	Yes	Adaptive	
	TLR7	Yes	Both	PAMP recognition
				Lysosomal pH optimization
	CXorf21	Yes	Both	
	FoxP3	No	Adaptive	Treg regulation
				T and B cell trafficking
6	CXCR3	Yes	Adaptive	
	NEMO *	No	Both	NF-kB activation
				Complement system - classical pathway
	C4	No	Innate	
	HLA	No	Adaptive	T cell antigen presentation

X-Linked Genes Associated with Sex Bias in Cancer or Autoimmune Diseases (1)

Gene	Y homologue gene	Xi status	Association with cancer sex bias	Association with autoimmune disease sex bias	Association with other sex bias
<i>ARHGEF6</i>	–	Inactive		X	
<i>ATRX</i>	–	Variable	X		
<i>BEND2</i>	–	Variable		X	
<i>C1GALT1C1</i>	<i>C1GALT1C1</i> pseudogene	Inactive/escape		X	
<i>CD40L</i>	–	Variable		X	
<i>CENP1</i>	<i>CENP1</i> pseudogene	Inactive		X	
<i>CNKSR2</i>	–	Variable	X		
<i>Cxorf21</i>	–	Escape		X	

X-Linked Genes Associated with Sex Bias in Cancer or Autoimmune Diseases (2)

Gene	Y homologue gene	Xi status	Association with cancer sex bias	Association with autoimmune disease sex bias	Association with other sex bias
<i>DDX3X</i>	<i>DDX3Y</i>	Escape	X		
<i>EFHC2</i>	–	Variable		X	
<i>FOXP3</i>	–	Inactive		X	
<i>GPR174</i>	–	Variable			X
<i>ITM2A</i>	–	Inactive		X	
<i>KDM5C</i>	<i>KDM5D</i>	Escape	X		
<i>KDM6A(UTX)</i>	<i>UTY</i>	Escape	X		
<i>MAGEC3</i>	–	Escape	X		

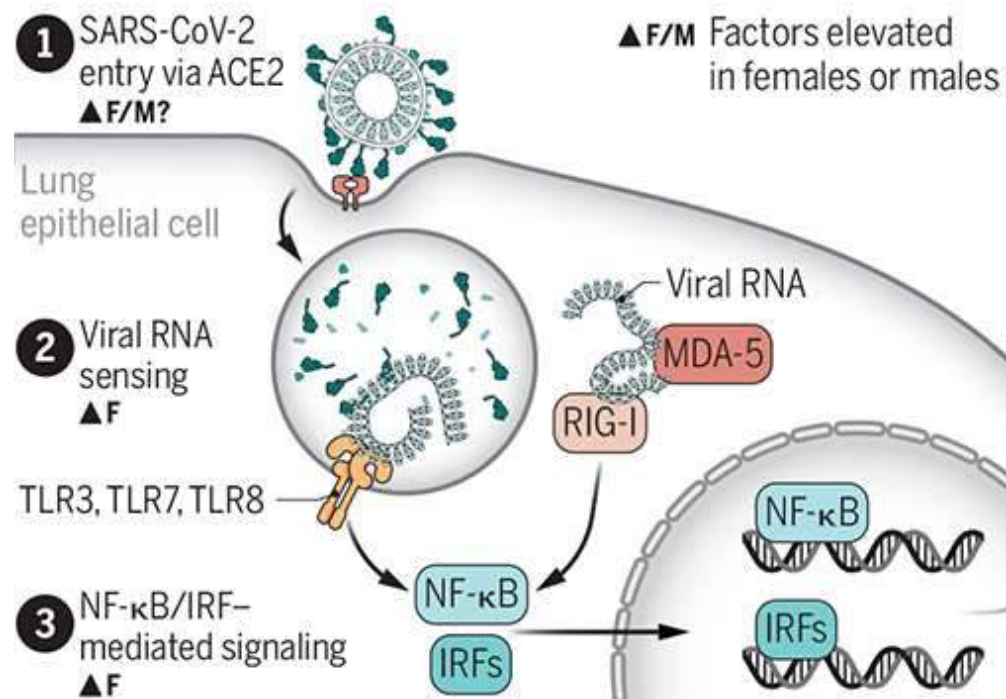
X-Linked Genes Associated with Sex Bias in Cancer or Autoimmune Diseases (3)

Gene	Y homologue gene	Xi status	Association with cancer sex bias	Association with autoimmune disease sex bias	Association with other sex bias
<i>MCF2</i>	–	Inactive		X	
<i>NAP1L2</i>	–	Inactive		X	
<i>NLGN4X</i>	<i>NLGN4Y</i>	Variable		X	X
<i>PPP1R3F</i>	–	Inactive		X	
<i>TLR7</i>	–	Inactive/escape		X	
<i>TMEM35</i>	–	Inactive		X	
<i>ZFX</i>	<i>ZFY</i>	Escape	X		

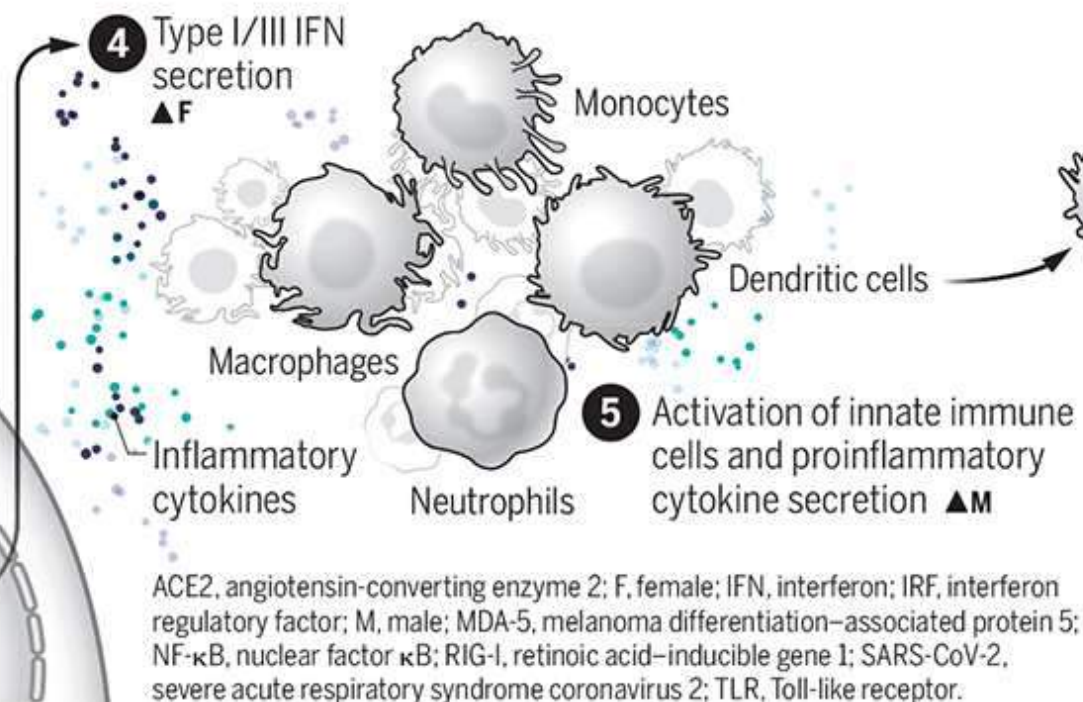
Sex differences in factors that affect infection and immunity in COVID-19

SARS-CoV-2 binds to ACE2 to initiate host cell entry. This activates the viral RNA sensors TLR3/7/8 and RIG-I–MDA-5, which induce secretion of IFNs and other inflammatory cytokines, leading to innate and adaptive immune responses. In each of these steps, sex differences may shape the antiviral immune response.

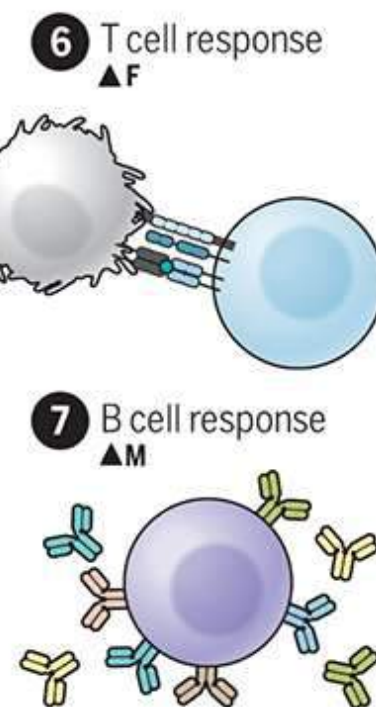
Viral entry, sensing, and cellular response



Innate immune response



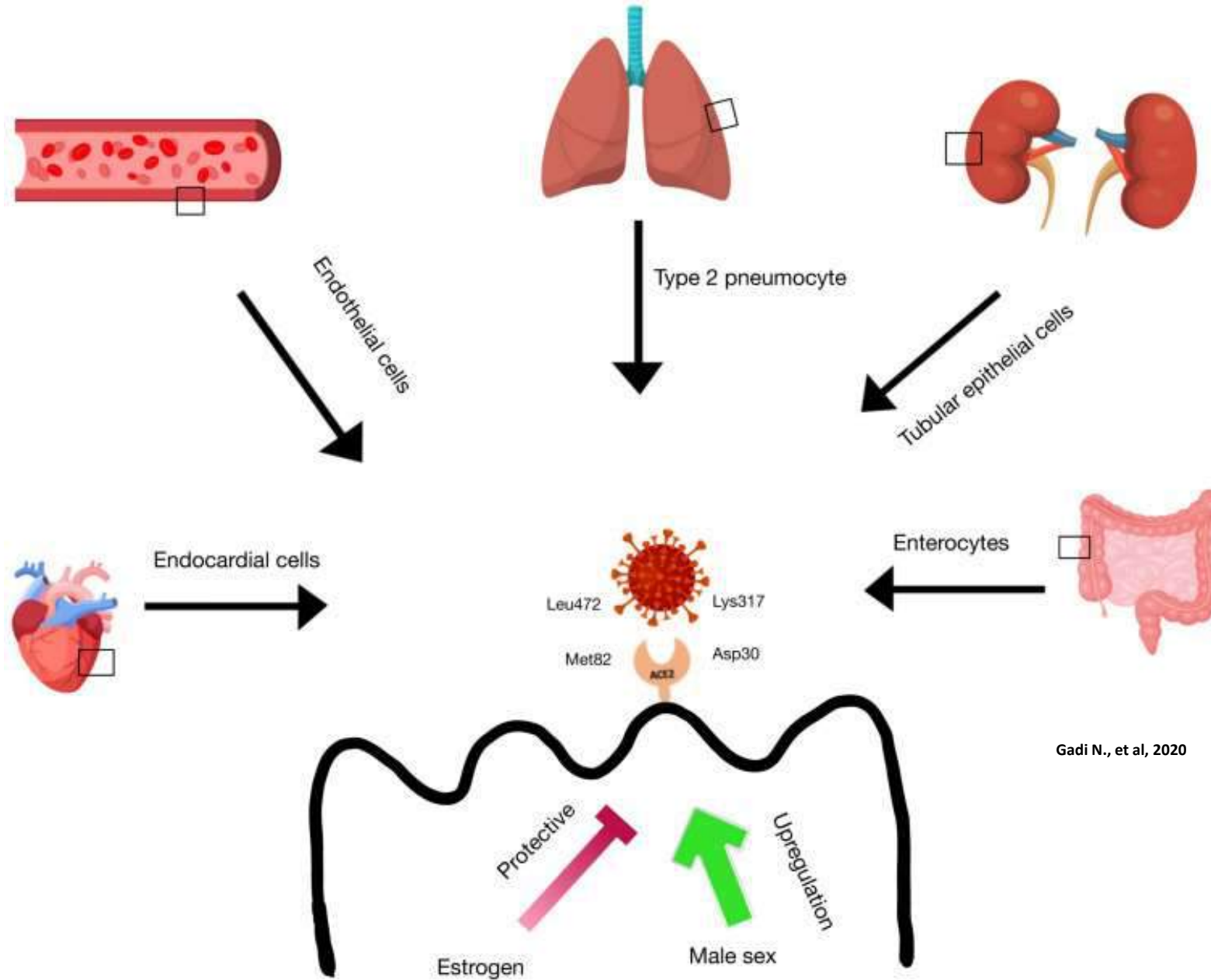
Adaptive immune response



Sex Hormones and their effects on immunity and relevance to COVID-19

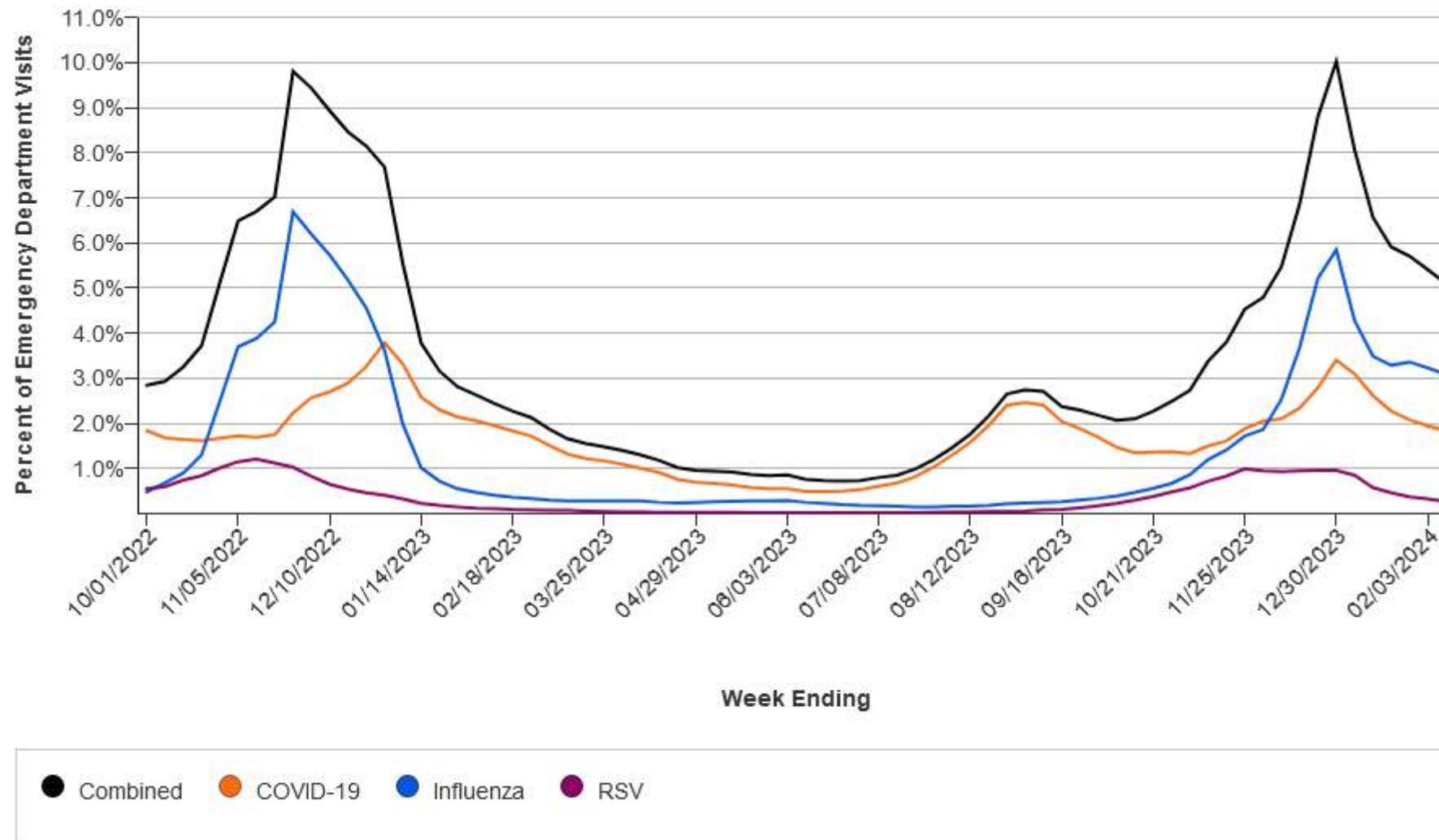
Hormone	Immune Cell/Cytokine	Effect	Relevance to COVID-19
Estrogen	Type 1 IFN	Promotes synthesis	Proinflammatory, beneficial early on but harmful when delayed
	IL-12	Promotes synthesis	Th1 cytokine, proinflammatory
	IL-6	Promotes synthesis	Pro-inflammatory (cytokine storm)
	IL-1 β	Promotes synthesis	Pro-inflammatory (cytokine storm)
	Neutrophils	Delays apoptosis	High recruitment and subsequent apoptosis are found in severe patients
	B cells	Promotes activation, maturation, differentiation, Ig antibody production	Beneficial IgG response but cytokine response is higher in women
	CD4 +	Promotes activation, Th1 differentiation	Different T cell types are needed for successful infection control
	Th17	Suppresses response	Th17 is proinflammatory, decreased levels means less host damage
	CD8 +	Increases activity	High levels early on may confer benefit
	Tregs	Increases FoxP3 expression and Treg production	Tregs suppress Th1 and Th17 responses and are anti-inflammatory
Progesterone	IL-10	Promotes synthesis	Anti-inflammatory, suppresses cytokine synthesis and MHC expression
	IL-1 β	Suppresses activation	Th1 cytokine, pro-inflammatory
	TNF	Suppresses activation	Pro-inflammatory, neutrophil and endothelial cell immune activation
	T cells	Decreases proliferation	May control T cell responses and cytokines
	IL-4	Increases production	Th2 cytokine, promotes Ig response controls T cell proliferation
	Tregs	Increases production	Tregs suppress Th1 and Th17 responses and are anti inflammatory
	Th17	Decreases production	Protects the host from adverse immune response
	CD8 +	Reduces IFN- γ production and cytotoxicity	Allows higher numbers of these cells without excess proinflammatory cytokines
Testosterone	TNF	Decreases production	Pro-inflammatory, neutrophil and endothelial cell immune activation
	IFN- γ	Decreases production	Pro-inflammatory, activates macrophages and increases antibody response
	IL-10	Increases production	Anti-inflammatory, suppresses cytokine synthesis and MHC expression

ACE2 receptor expression in tissues



Virus respiratori: SARS-CoV2, Influenza e
Virus Respiratorio Sinciziale (RSV)

Casi di virus respiratori negli USA

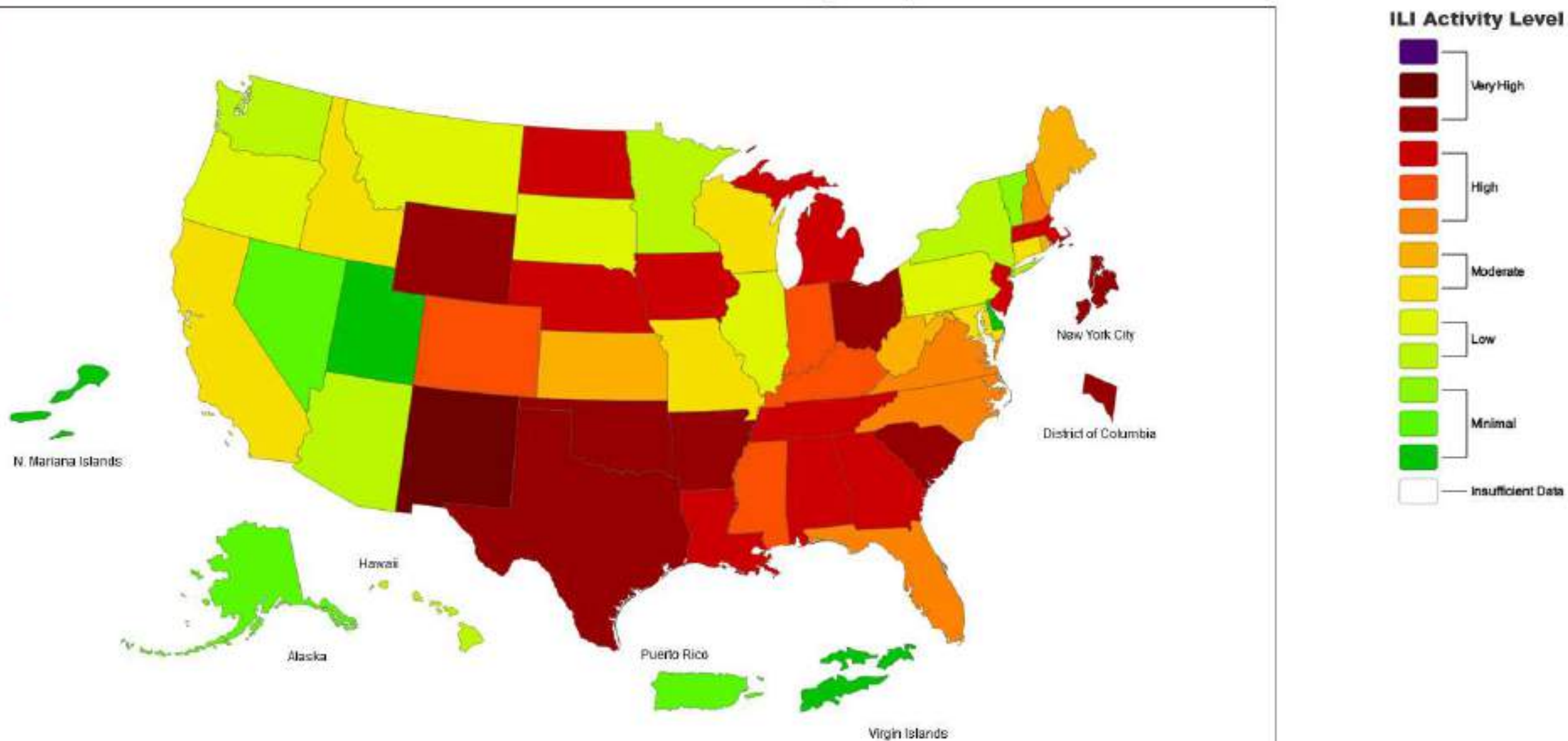


Data presented through: 02/10/2024; Data as of: 02/14/2024

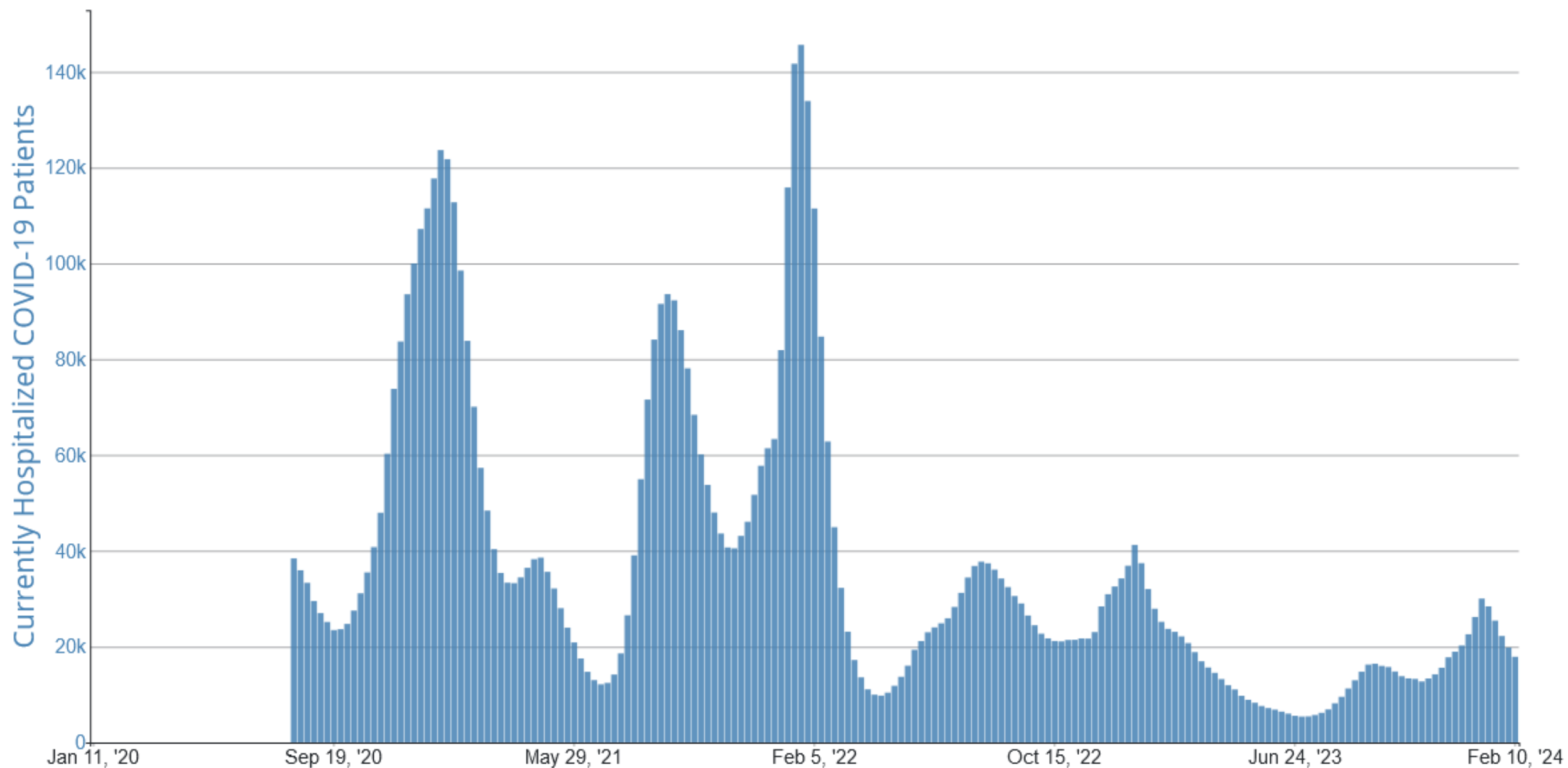


Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

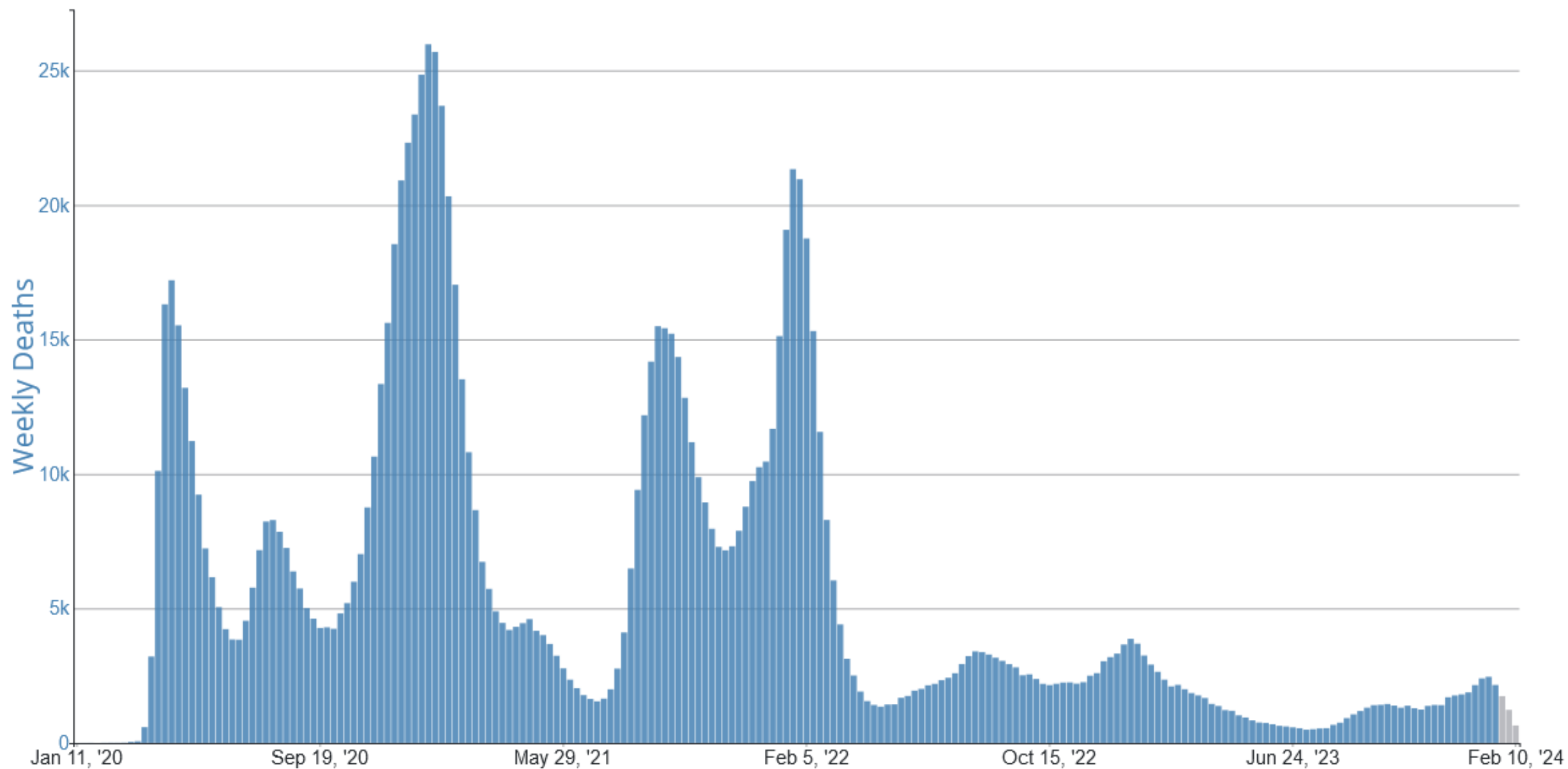
2023-24 Influenza Season Week 6 ending Feb 10, 2024



Currently Hospitalized Patients with Confirmed COVID-19, by Week, in The United States, Reported to CDC



Provisional COVID-19 Deaths, by Week, in The United States, Reported to CDC



COVID-19 Update for the United States

Early Indicators

Test Positivity >

% Test Positivity

9.3%

(February 4 to February 10, 2024)

Trend in % Test Positivity

-0.6% in most recent week



Dec 23, 2023

Feb 10, 2024

Emergency Department Visits >

% Diagnosed as COVID-19

1.8%

(February 4 to February 10, 2024)

Trend in % Emergency Department Visits

-5.3% in most recent week



Dec 23, 2023

Feb 10, 2024

These early indicators represent a portion of national COVID-19 tests and emergency department visits. [Wastewater](#) information also provides early indicators of spread.

Severity Indicators

Hospitalizations >

Hospital Admissions

21,373

(February 4 to February 10, 2024)

Trend in Hospital Admissions

+0.8% in most recent week



Dec 23, 2023

Feb 10, 2024

Total Hospitalizations

6,816,249

Deaths >

% of All Deaths in U.S. Due to COVID-19

2.7%

(February 4 to February 10, 2024)

Trend in % COVID-19 Deaths

-6.9% in most recent week



Dec 23, 2023

Feb 10, 2024

Total Deaths

1,178,527

CDC | Test Positivity data through: February 10, 2024; Emergency Department Visit data through: February 10, 2024; Hospitalization data through: February 10, 2024; Death data through: February 10, 2024.

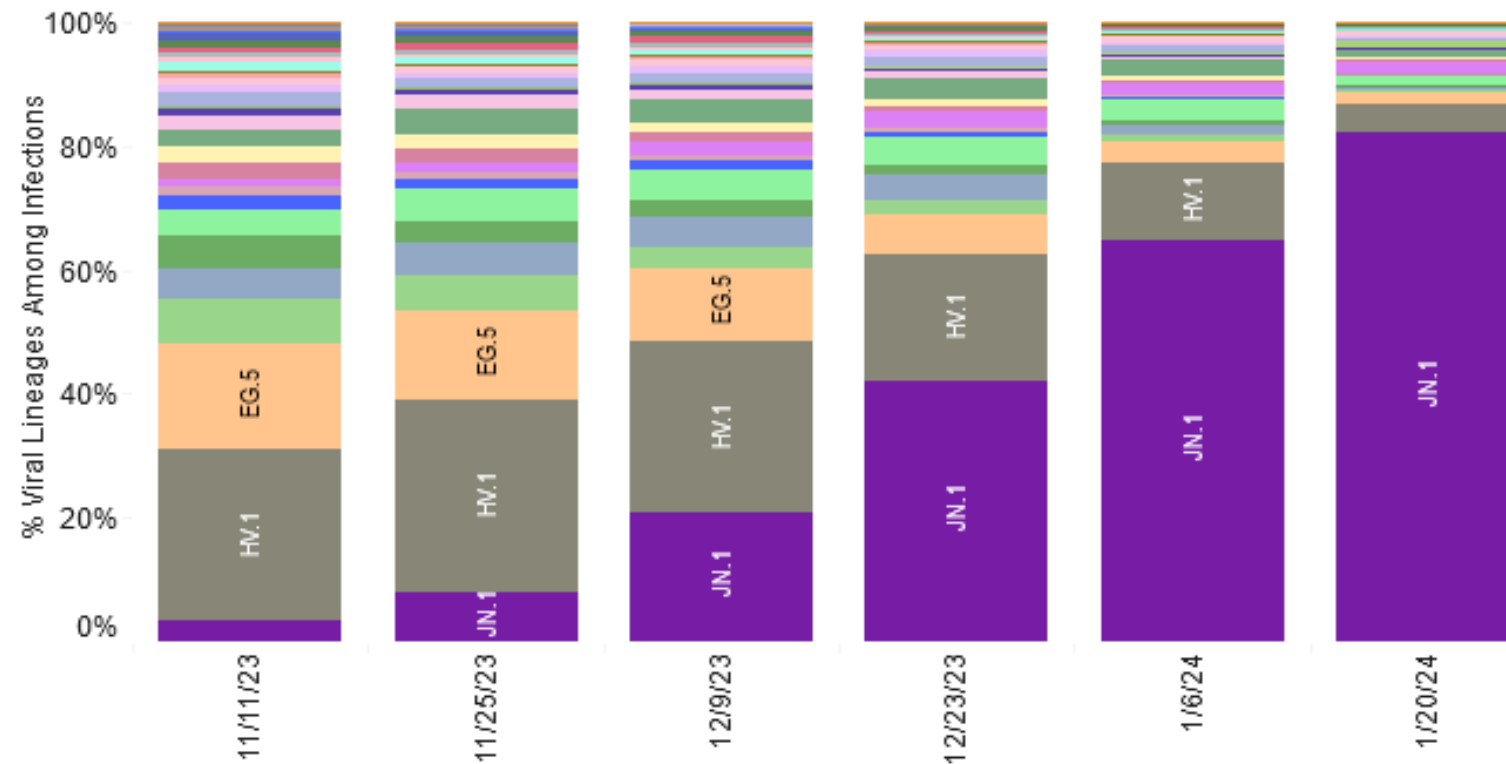
Posted: February 16, 2024 12:16 PM ET

Weighted and Nowcast Estimates in United States for 2-Week Periods in 10/29/2023 – 2/17/2024

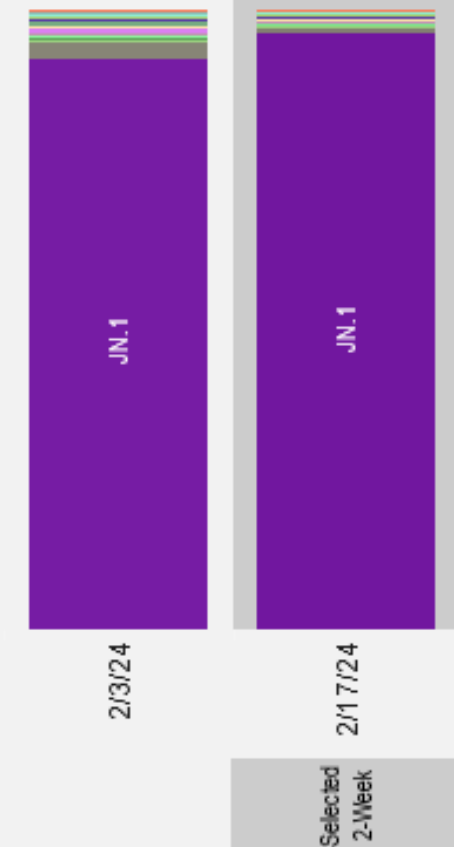


Hover over (or tap in mobile) any lineage of interest to see the amount of uncertainty in that lineage's estimate.

Weighted Estimates: Variant proportions based on reported genomic sequencing results



Nowcast: Model-based projected estimates of variant proportions



Collection date, 2-week period ending

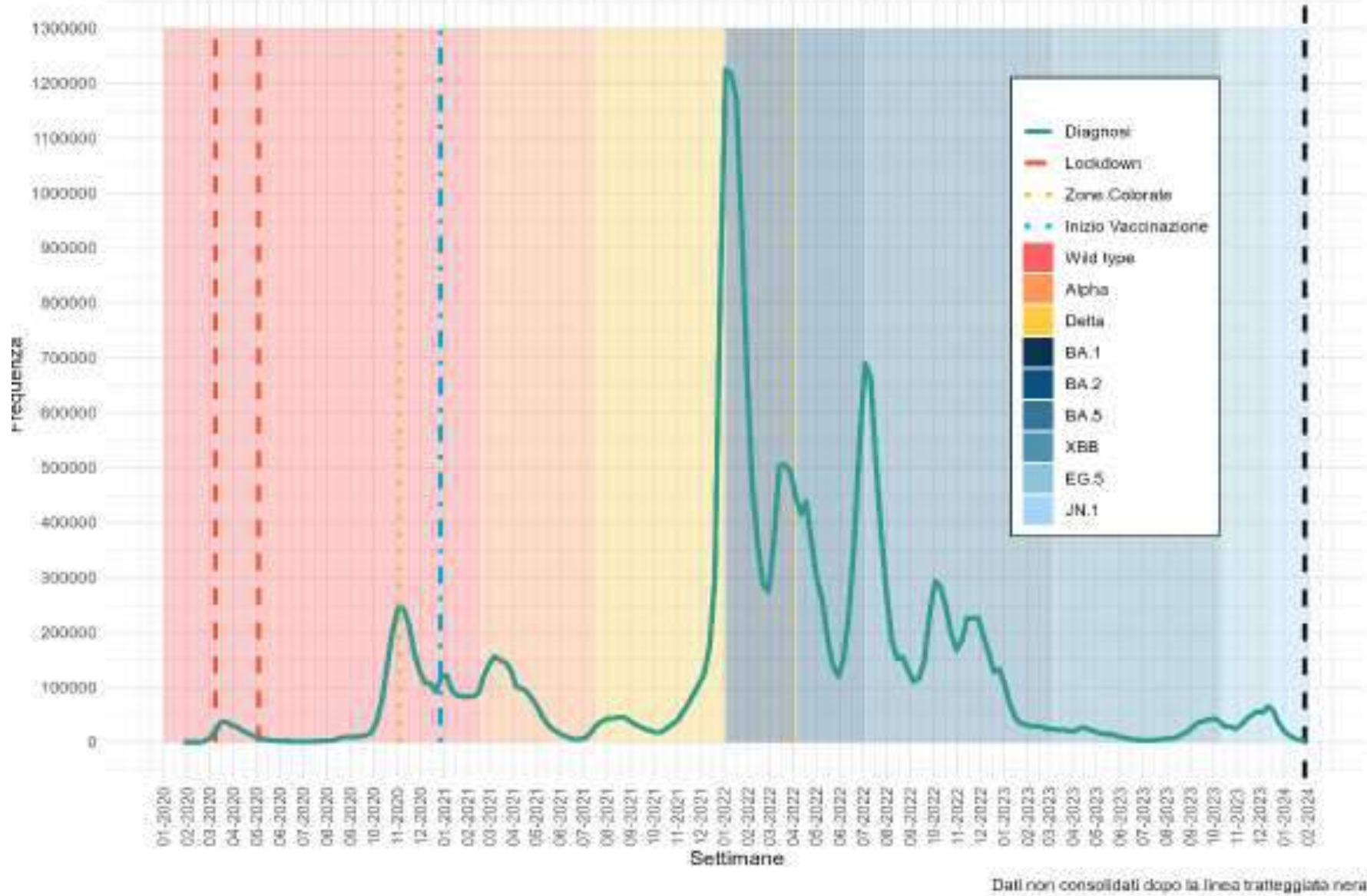


Figura 1 - Numero settimanale di diagnosi di infezione da SARS-CoV-2 segnalate in Italia per settimana prelievo/diagnosi da inizio pandemia

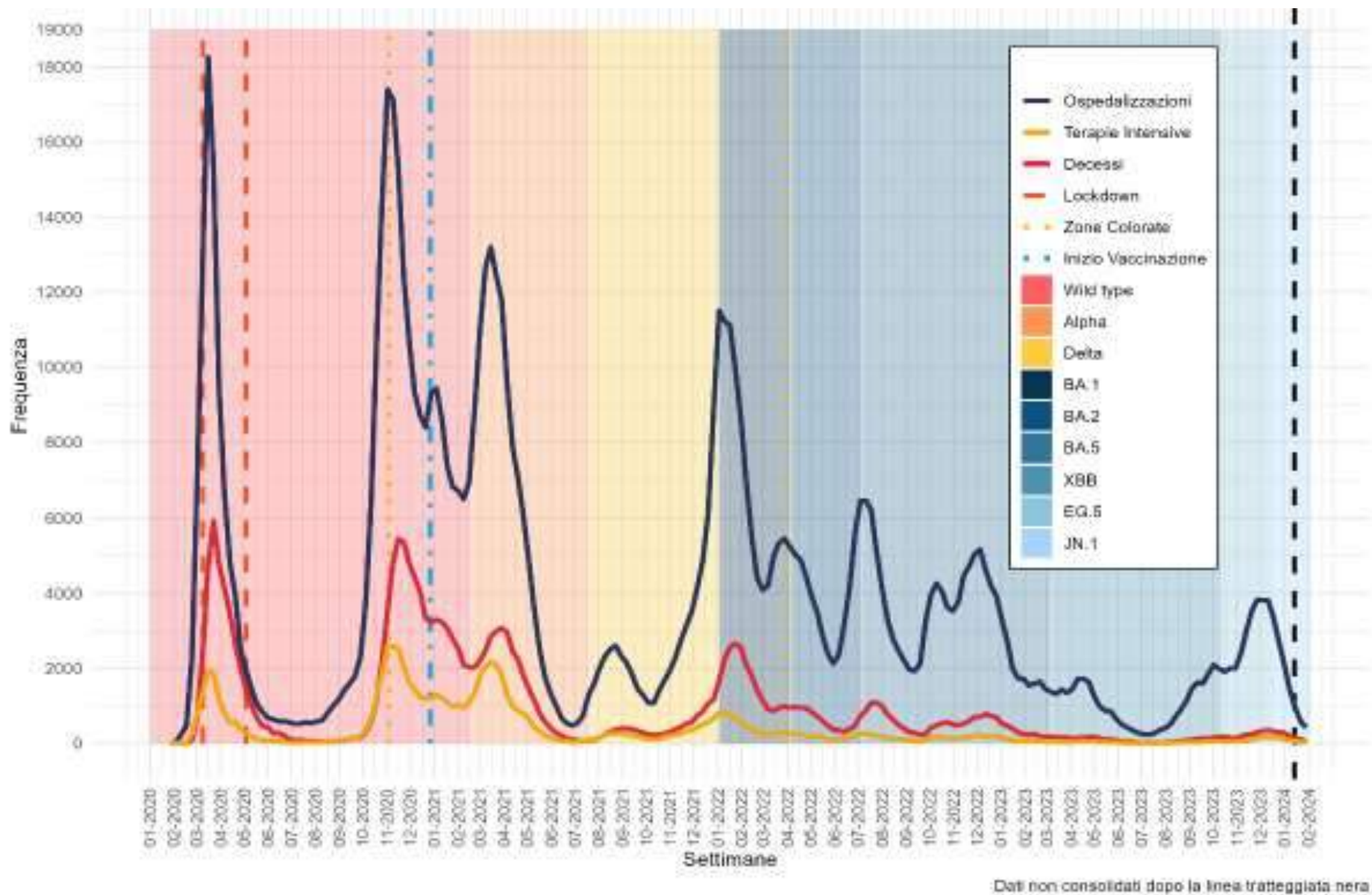


Figura 10 - Numero settimanale di ospedalizzazioni, terapie intensive e decessi per settimana dell'evento da inizio pandemia



Nota: il dato relativo all'ultima settimana non è completamente consolidato e potrebbe essere soggetto a lievi variazioni.

Figura 6 - Tasso di incidenza di infezioni da SARS-CoV-2 (per 100.000 ab.) segnalate in Italia per provincia (Periodo: 29/01 - 04/02/2024)

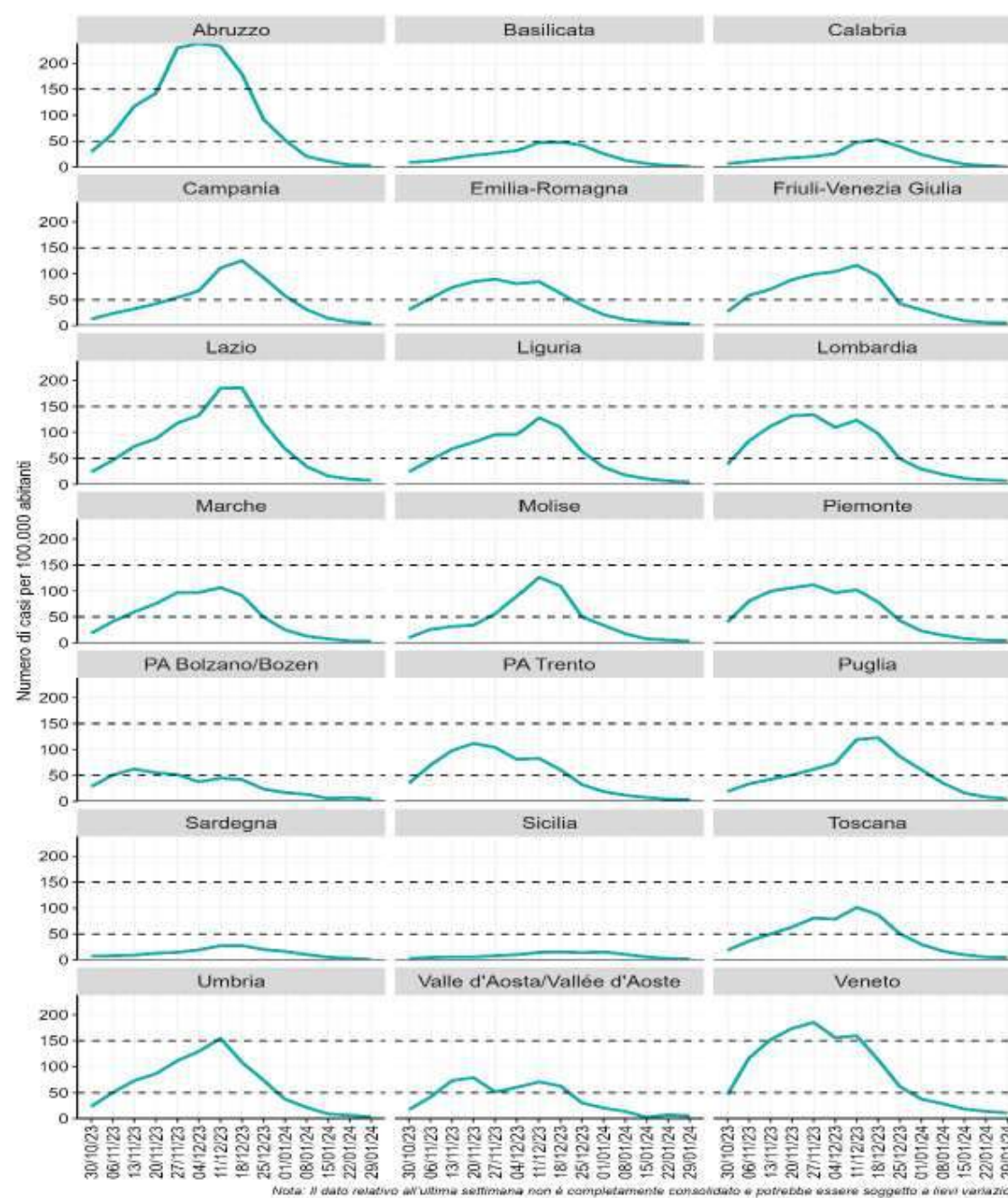
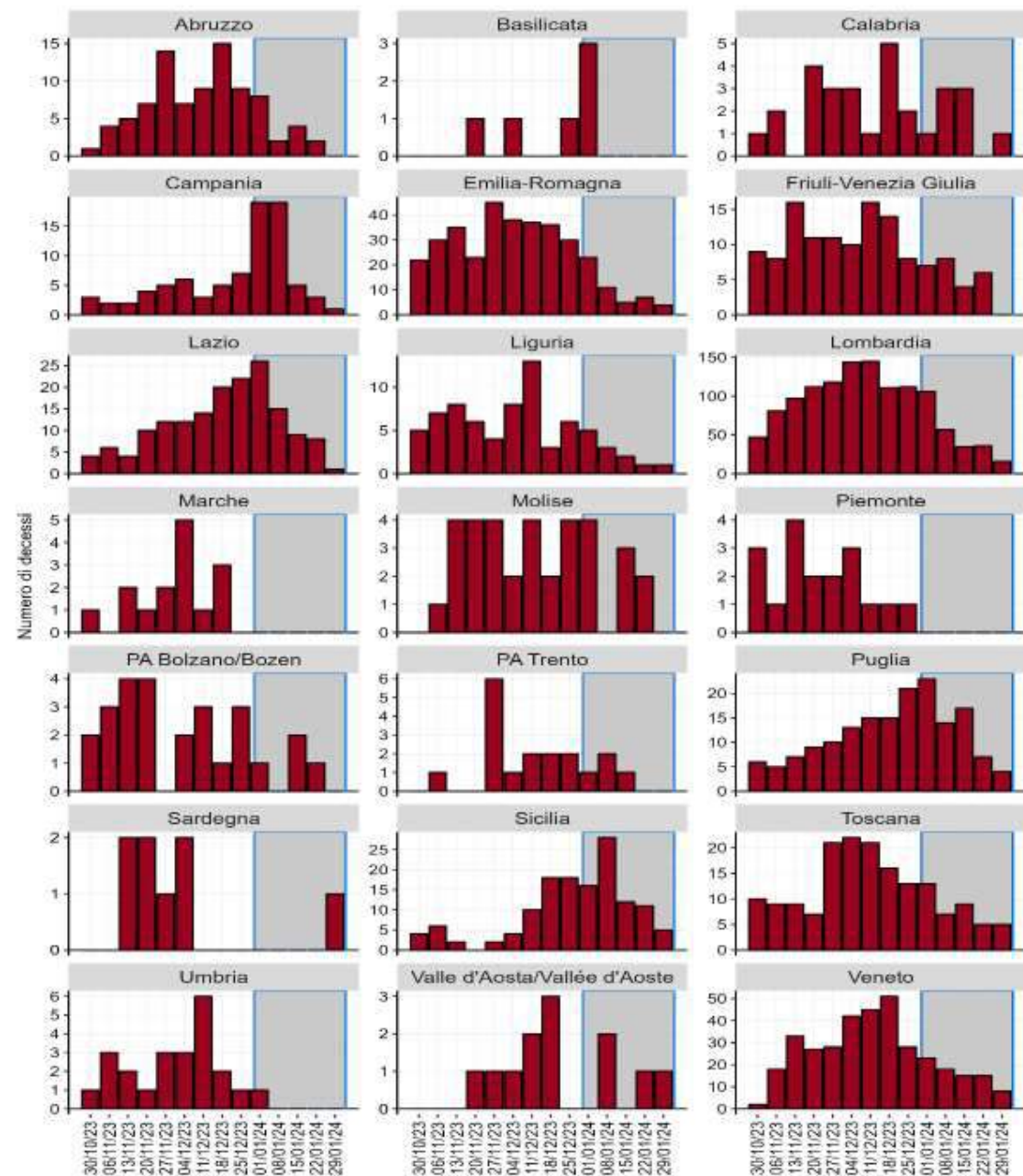


Figura 16 - Incidenza settimanale di diagnosi di infezioni per SARS-CoV-2 (per 100.000 ab.) per Regione/PPAA dal 30 ottobre 2023



Nota: Il dato nell'area grigia relativo alle ultime quattro settimane non è consolidato e verosimilmente sottostimato

Figura 19 - **Decessi** settimanali per Regione/PPAA dal 30 ottobre 2023

Monitoraggio delle varianti di SARS-CoV-2

**Tabella 2 - Stime di prevalenza delle principali varianti di SARS-CoV-2 in Italia
(casi notificati dal 15 al 21 gennaio 2024)**

Lignaggio	Prevalenza (%)	Range prevalenza (%) per Regione/PA
JN.1	77,0%	(0,0 - 100%)
EG.5	7,3%	(0,0 - 100%)
BA.2.86	6,1%	(0,0 - 100%)
XBB.1.9	1,7%	(0,0 - 25,0%)
XBB.1.16	0,4%	(0,0 - 4,2%)
XBB.2.3	0,2%	(0,0 - 11,1%)
XBB.1.5	0,2%	(0,0 - 3,7%)

Nota: I lignaggi riportati comprendono i relativi sotto-lignaggi non soggetti a classificazione specifica ([ECDC](#), [WHO](#)).

The background of the slide is a composite of microscopic images. On the left, there's a large, semi-transparent circular area containing a pinkish-red cellular structure. To the right, there are various other cellular and viral structures in shades of blue, purple, and red, some appearing to be covered in small, white, circular particles, possibly representing viral particles or cellular components.

Grazie dell'attenzione

Davide Zella, PhD

- Assistant Professor of Biochemistry and Molecular Biology
- Co-Head, Laboratory of Tumor Cell Biology
- Institute of Human Virology
- University of Maryland, School of Medicine