Vaccine induction of trained immunity: mechanisms and new insights

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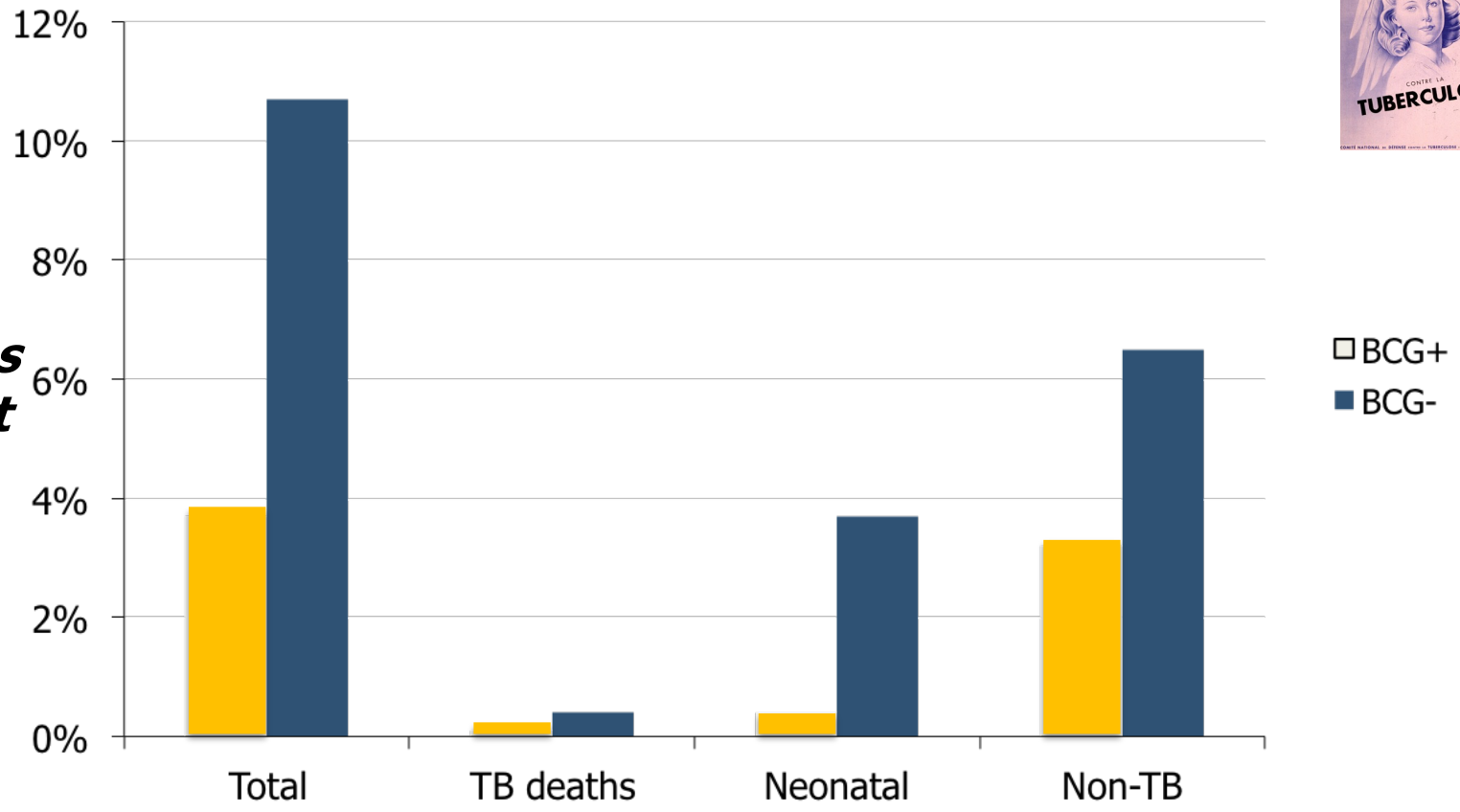
Introducing BCG in Norrbotten, Sweden, 1927-31

Coverage highest in families with TB

Reduction was in infancy, but TB deaths occur later

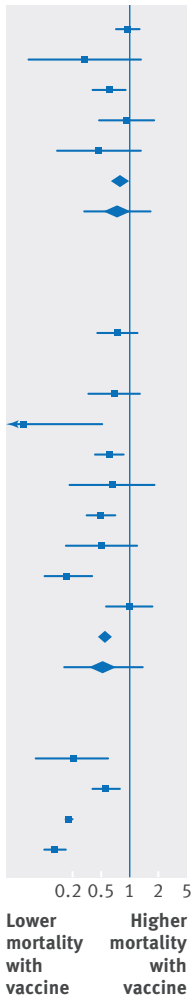
This made little sense



"One could evidently be tempted to find an explanation for this much lower mortality among vaccinated children in the idea that BCG provokes *a **non-specific immunity**...*"
Carl Naeslund 1932

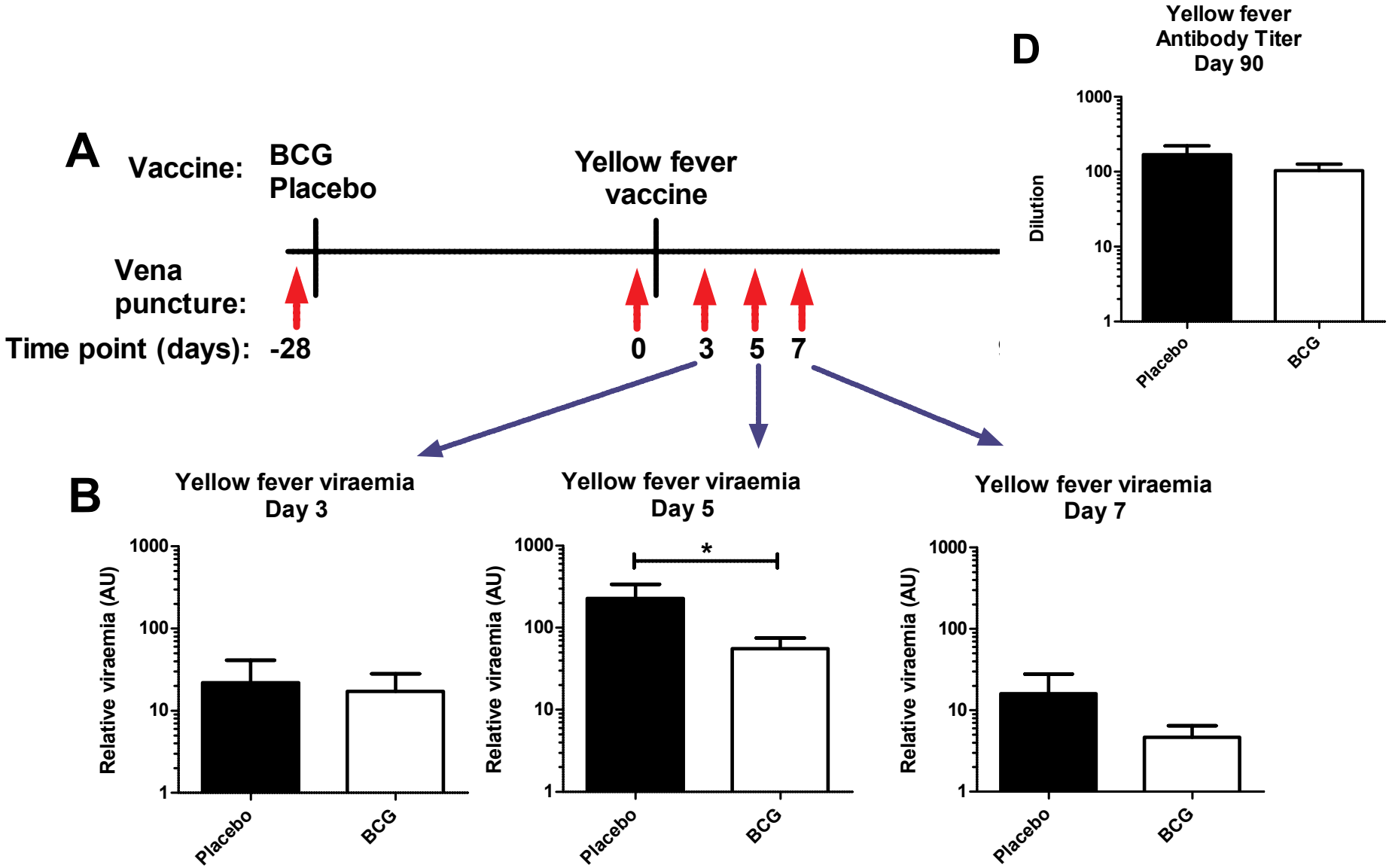
WHO-SAGE report: BCG protects against all-cause mortality

Birth cohort	Deaths/ children*	Subsequent DTP†	Subsequent MV‡	Age at first dose	Observation period§	Effect measure	Adjustment	Relative risk (95% CI)	Relative risk (95% CI)	Mortality reduction¶	Assessment of risk of bias
Clinical trials											
Canada 1933-45[a4]	(53+63)/609	None	None	10 days	Age 60 months	RR	None		0.94 (0.67 to 1.32)	6% (-32% to 33%)	Moderate risk
Guinea-Bissau 2002-08 (early)**[a14]	(2+6)/105	None	None	2 days	Age 1 month	HR	Age		0.28 (0.06 to 1.37)	72% (-37% to 94%)	Low risk
Guinea-Bissau 2002-08 (main)[a16]	(27+48)/2343	None	None	2 days	Age 1 month	MRR	Age		0.55 (0.34 to 0.89)	45% (11% to 66%)	Low risk
USA c.1935[a26]	(12+13)/3008	None	None	0-4 years	Age 48 months	MRR	None		0.91 (0.41 to 1.99)	9% (-99% to 59%)	Moderate risk
USA c.1941[a27]	(4+9)/451	None	None	7-10 days	Age 60 months	RR	None		0.42 (0.13 to 1.35)	58% (-35% to 87%)	Moderate risk
FE subtotal: P=0.20, I^2=33%									0.76 (0.59 to 0.97)		
RE subtotal									0.70 (0.49 to 1.01)		
with estimated predictive interval									(0.27 to 1.81)		
Observational studies											
Case-control											
Benin 1983-87[a2]	(34+39)/294	Many	Many	NR	Age 4-36 months	OR	Age, sex, others		0.68 (0.38 to 1.23)	32% (-23% to 62%)	High risk
Cohort											
Guinea-Bissau 1984-87[a6]	NR/1657	Many	Some	NR (0-8 months)	Age 8 months	HR	Age, sex, DTP, others		0.63 (0.30 to 1.33)	37% (-33% to 70%)	High risk
Guinea-Bissau 1989-2001[a7]	(2+14)/695	Many	Few	1-7 days	Age 6 months	HR	Age, sex, others		0.05 (0.01 to 0.46)	95% (54% to 99%)	High risk
Guinea-Bissau 1990-96[a10]	(92+97)/4418	Many	Some	Median 1 month	6 months follow-up	HR	Age, DTP, others		0.56 (0.37 to 0.84)	44% (16% to 63%)	High risk
India 1987-89[a19]	(3+29)/3072	None	Some	Median 1.6 months	Age 12 months	MRR	None		0.60 (0.18 to 1.97)	40% (-97% to 82%)	High risk
India 1998-2002[a20]	208/10 274	Many [c]	Few	Median 19 days	Age 6 months	HR	Age		0.44 (0.29 to 0.66)	56% (34% to 71%)	High risk
Malawi 1995-97[a22]	NR/751	Many [c]	Few	Median 16 days	Age 8 months	HR	Age, others		0.45 (0.16 to 1.23)	55% (-23% to 84%)	High risk
Papua New Guinea 1989-94[a23]	NR/3937	Many	Few	Median 1 month	Age 1-6 months	HR	Age, DTP, others		0.17 (0.09 to 0.34)	83% (66% to 91%)	High risk
Senegal 1996-99[a24]	(9+372)/4421	Many [c]	Many [c]	NR (by 12 months in 44%)	Age 24 months	HR	Age, others		0.98 (0.50 to 1.90)	2% (-90% to 50%)	High risk
FE subtotal: P=0.005, I^2=63%									0.49 (0.40 to 0.61)		
RE subtotal									0.47 (0.32 to 0.69)		
with estimated predictive interval									(0.15 to 1.46)		
Excluded (very high risk of bias)											
Bangladesh 1986-2001[a1]	184/37894	Many (OS)	Many	0-2 months	Age 0-60 months	HR	Age		0.20 (0.07 to 0.54)		Very high risk
Burkina Faso 1985-93[a3]	(28+280)/9085	Many (SS)	Many [cens]	Mean 4.8 months	6 months follow-up	HR	Age, others		0.50 (0.34 to 0.75)		Very high risk
Ghana 1998-2004[a5]	NR/17 967	Many	Many	NR (by 12 months in 57%)	Age 60 months	HR	Age, others		0.18 (0.17 to 0.20)		Very high risk
India 2006-11[a21]	(45+285)/11 390	Few	None	Mean 17 days	Age 1.2 months	MRR	None		0.12 (0.09 to 0.16)		Very high risk



Higgins et al, BMJ, 2016

BCG vaccination in vivo & yellow fever vaccine



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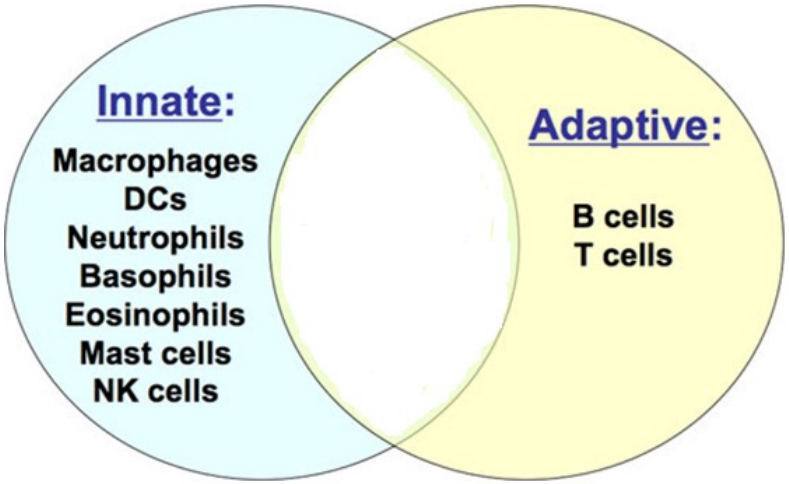
Arts et al, Cell Host Microbe, 2018

Innate versus specific immunity



Innate immunity:

- rapid
- effective
- not-specific, indiscriminate
- lacks immunological memory

Adaptive immunity:

- needs 10-14 days
- specific activation against a particular microorganism, enhancing the effect of the response
- builds immunological memory

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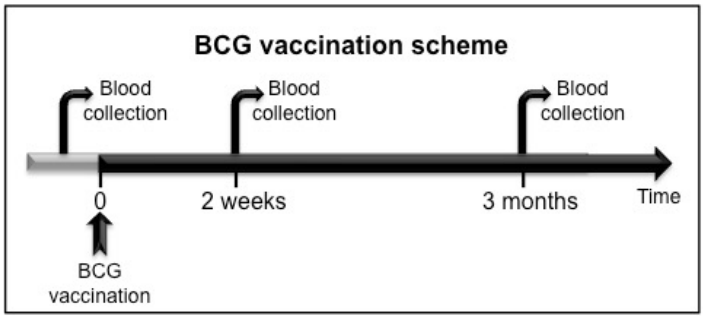
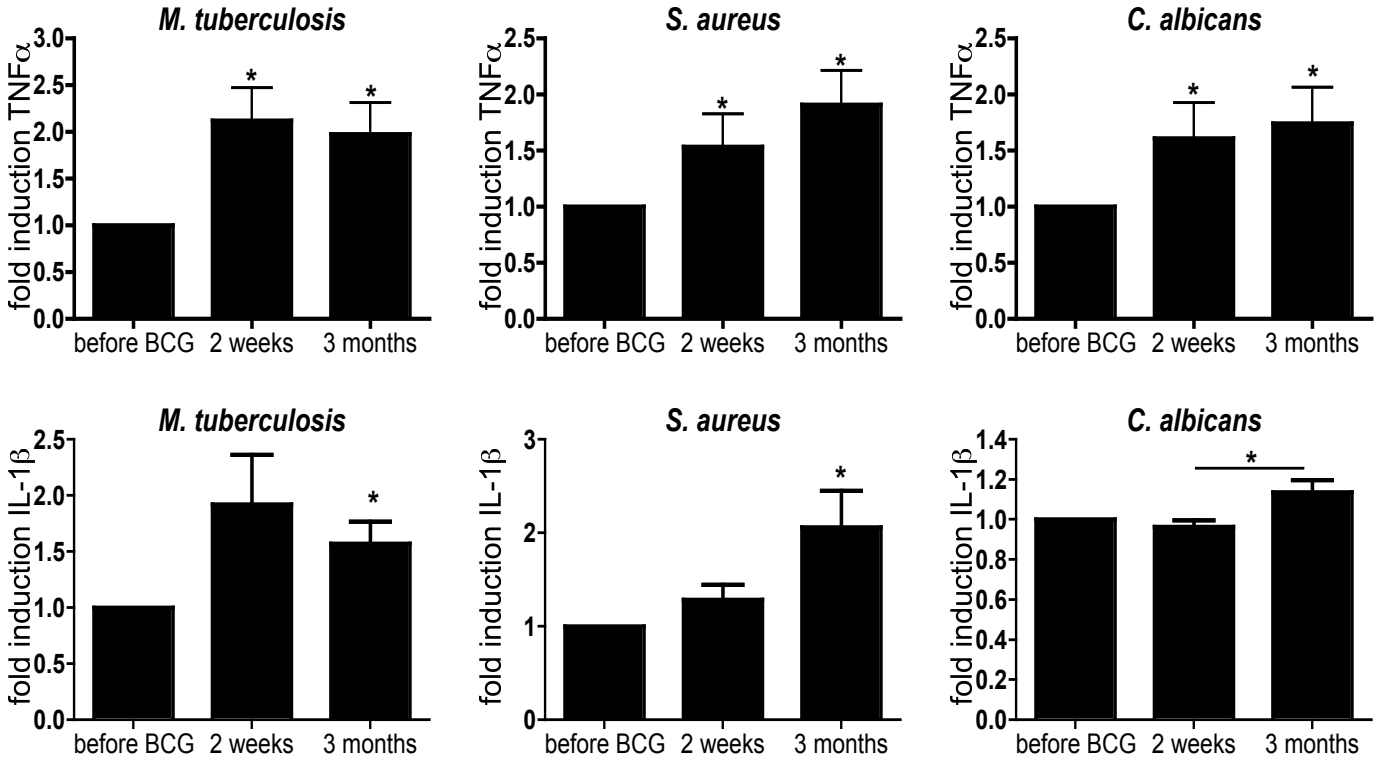
BCG enhances monocyte-derived cytokines





Kleinnijenhuis et al, PNAS, 2012

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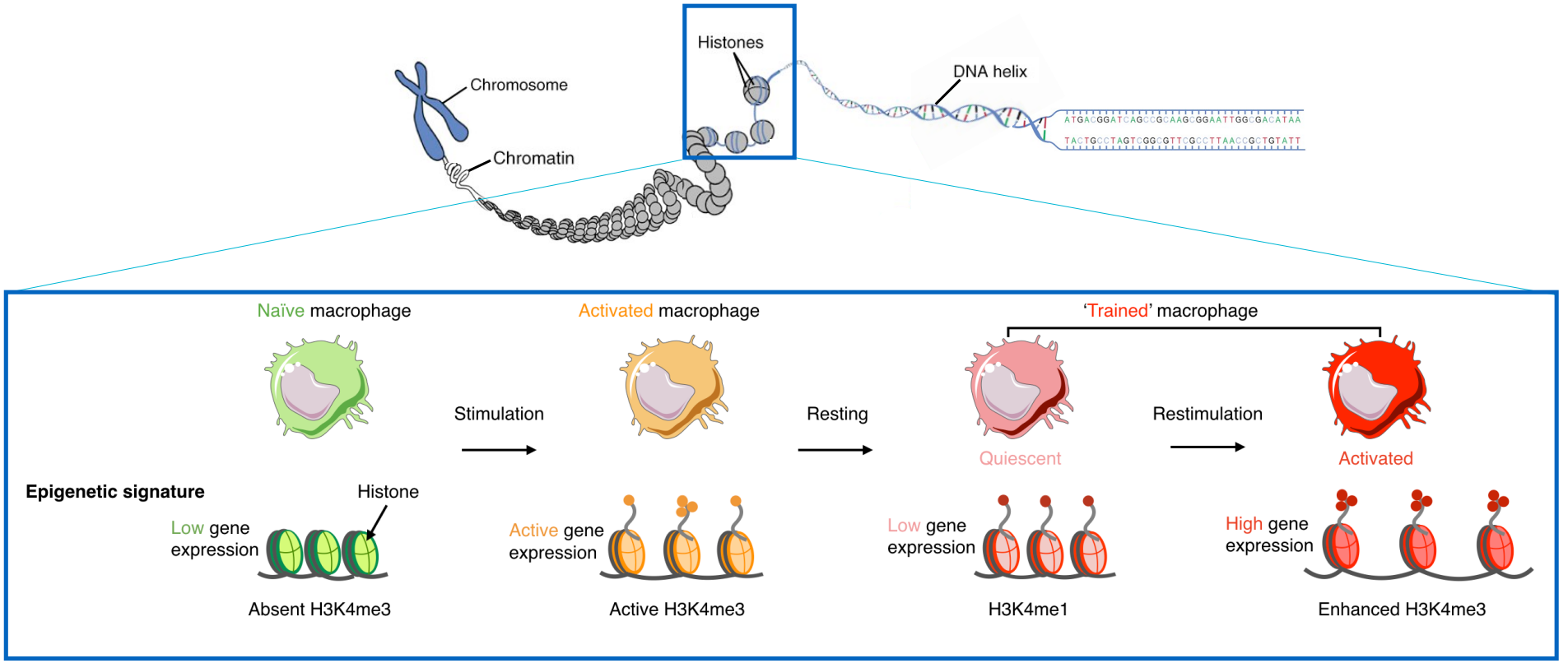
Long-term epigenetic reprogramming in myeloid cells



Resting | **Infection** | **Resting** | **Re-infection**

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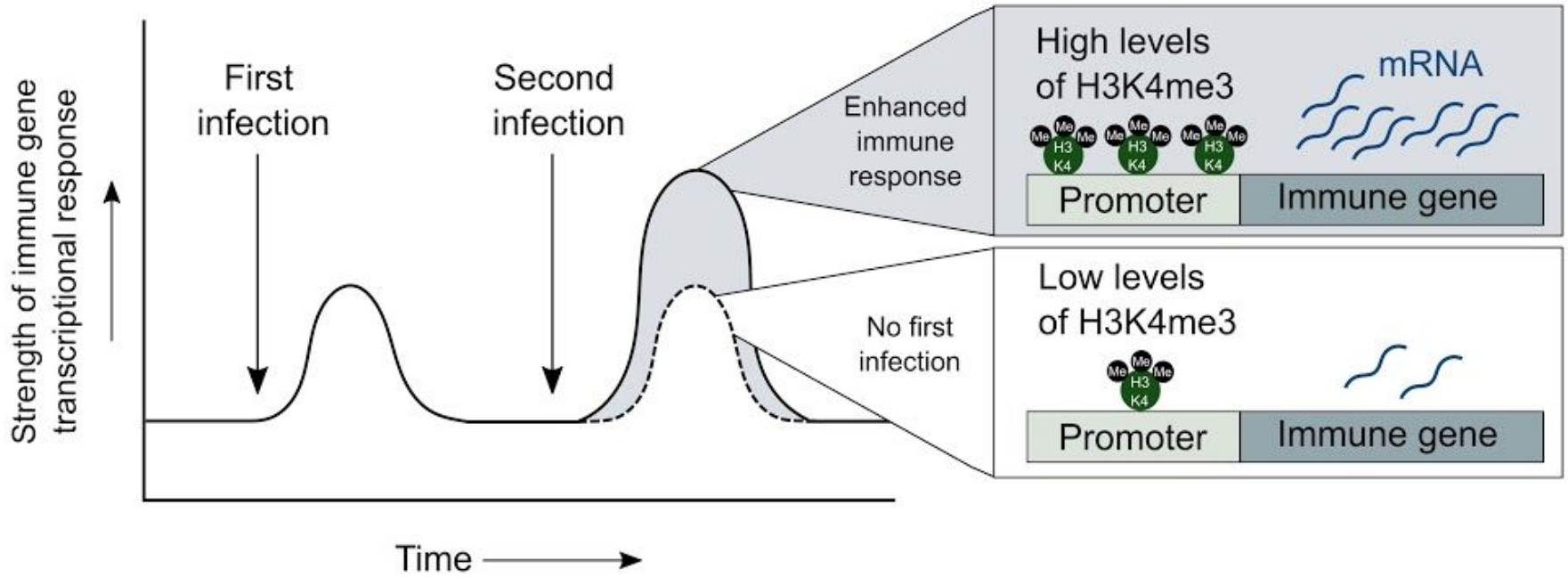
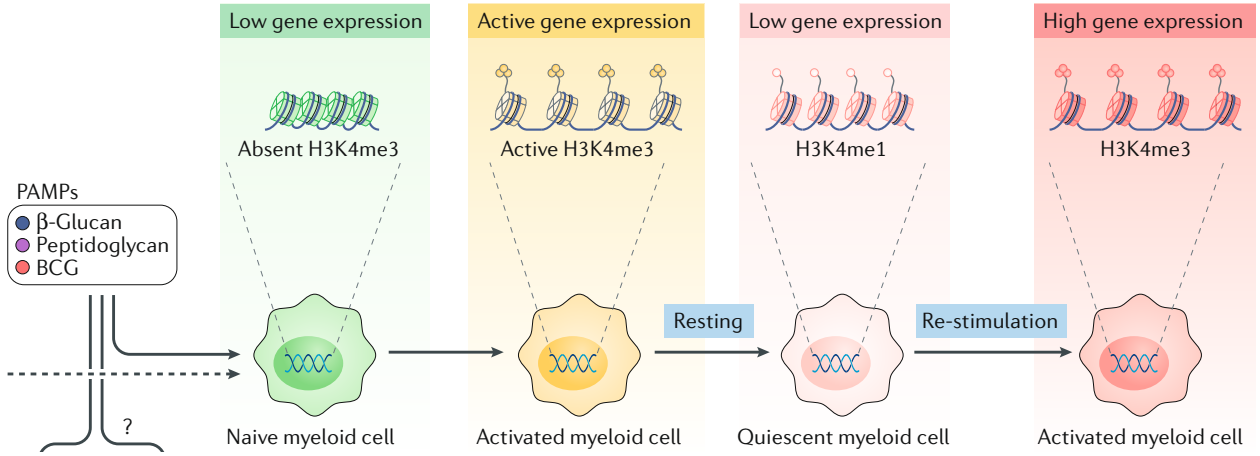
Long-term epigenetic reprogramming in myeloid cells





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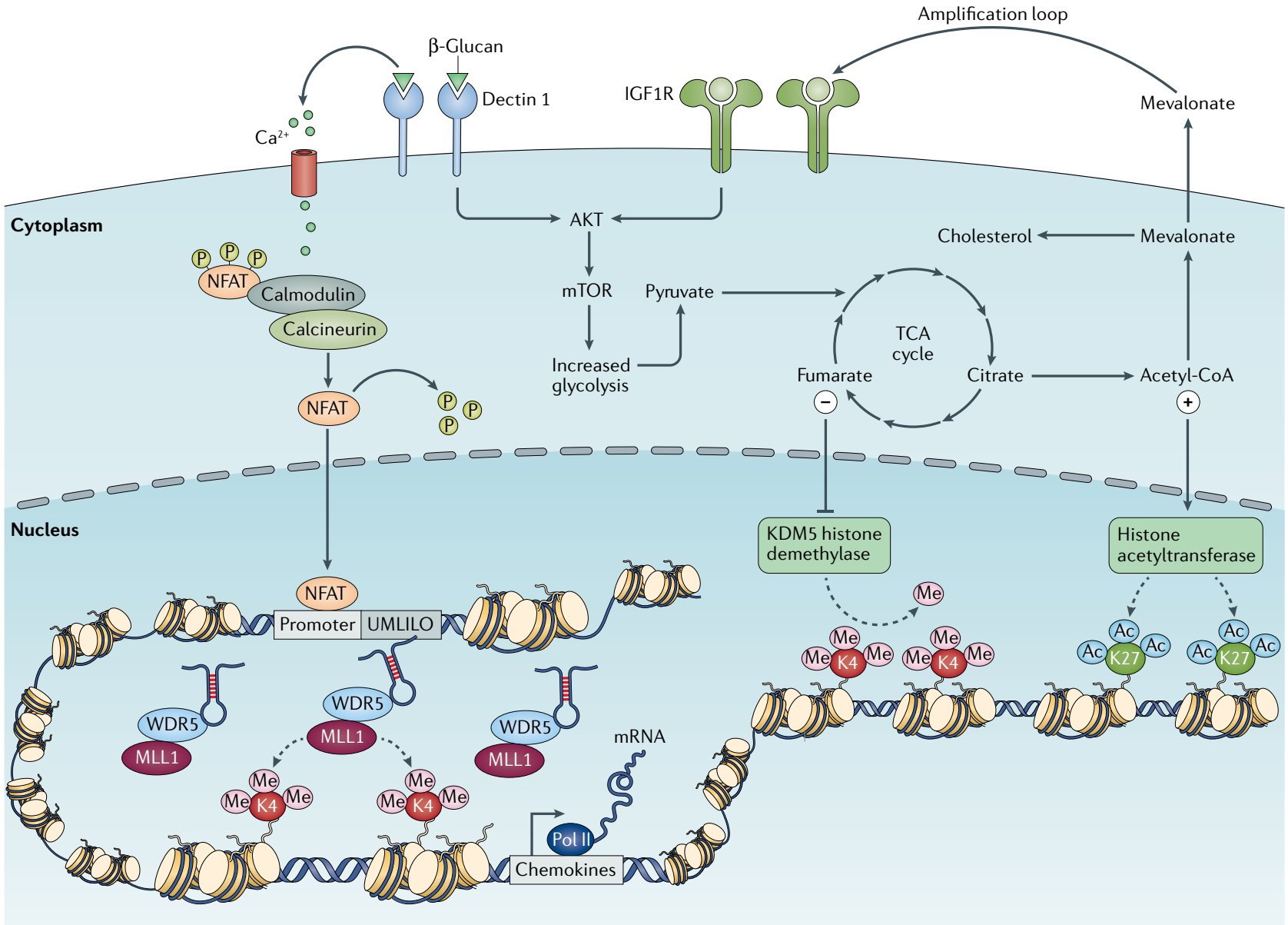
Trained immunity: mechanisms



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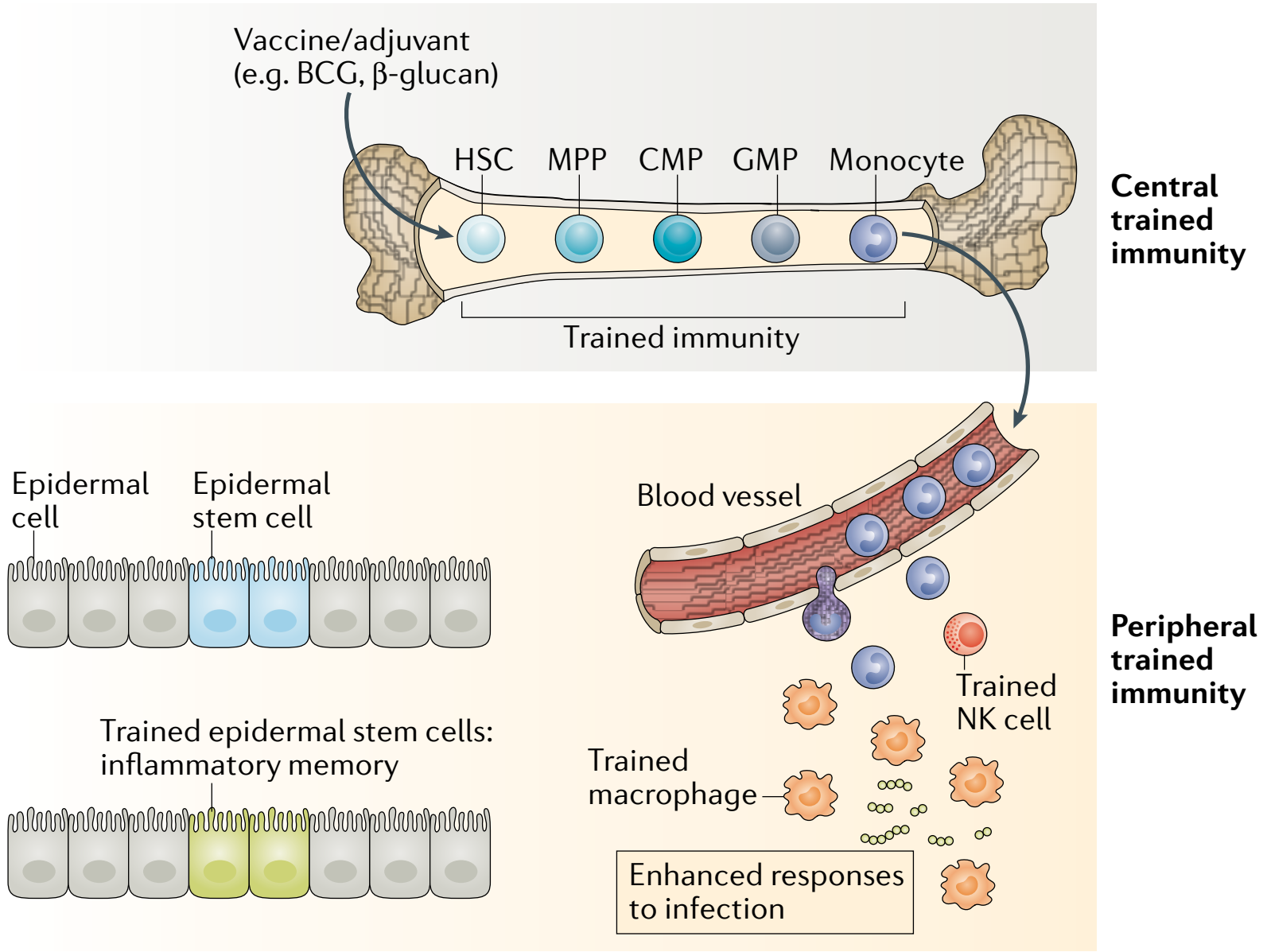
Netea et al, Nature Rev Immunol 2020

Trained immunity: from bone marrow to local defenses



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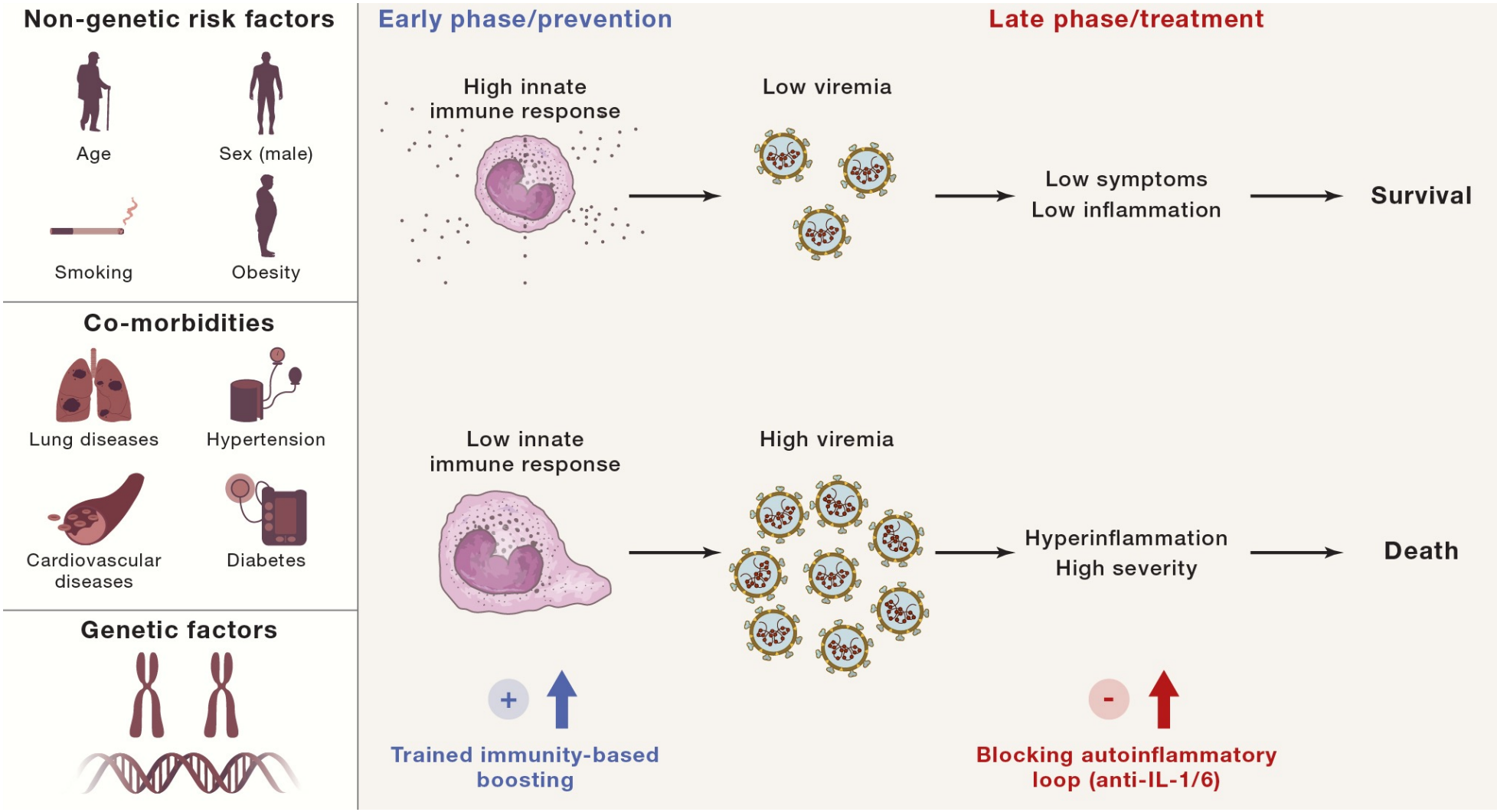
Netea et al, Nature Rev Immunol 2020

COVID-19: infection and pathophysiology



Netea et al, Cell 2020

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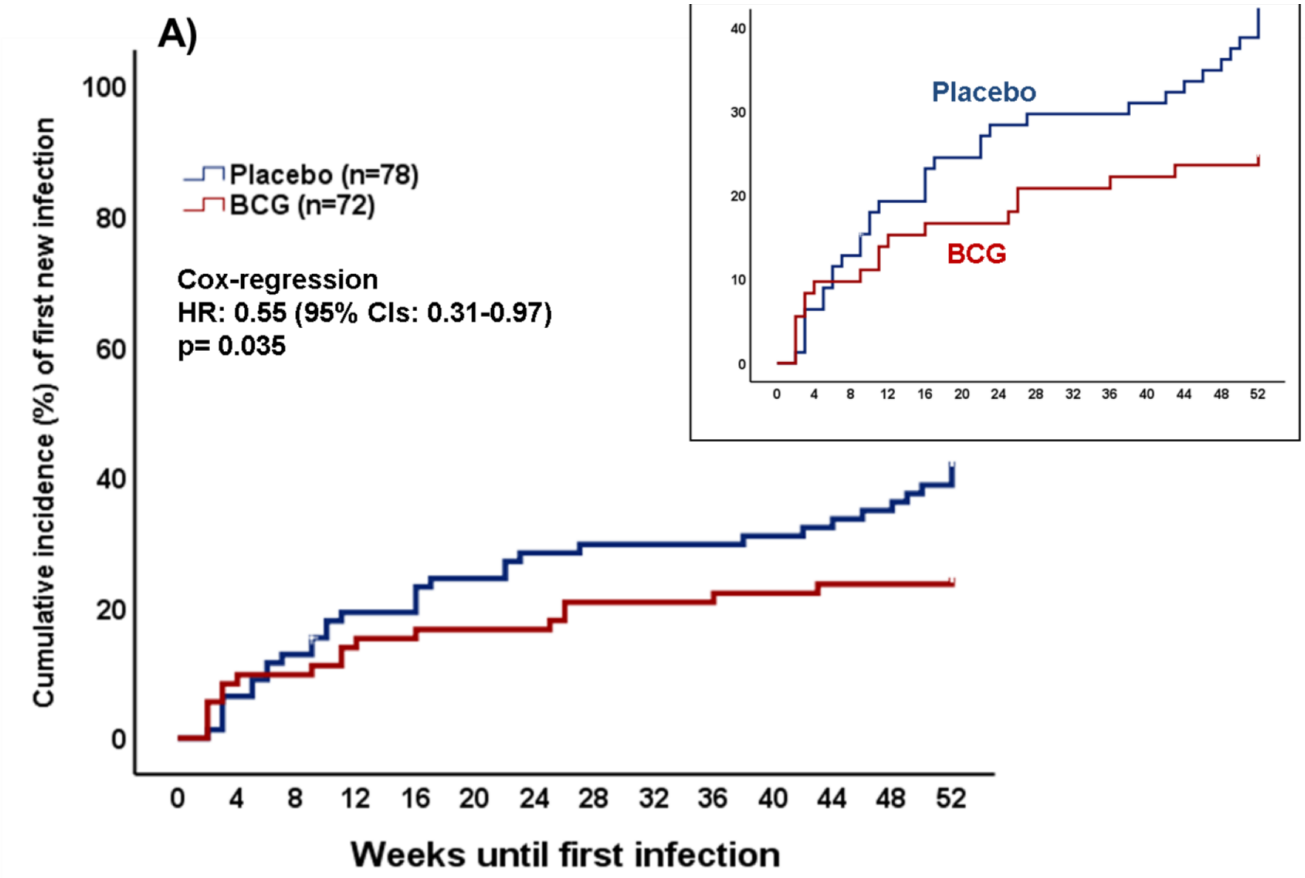
ACTIVATE study: BCG in elderly



No of pts at risk	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Placebo	78	73	68	62	59	58	55	54	54	54	53	51	49	45
BCG	72	65	65	61	60	60	60	57	57	56	56	55	55	54

Giamarellos et al, Cell 2020

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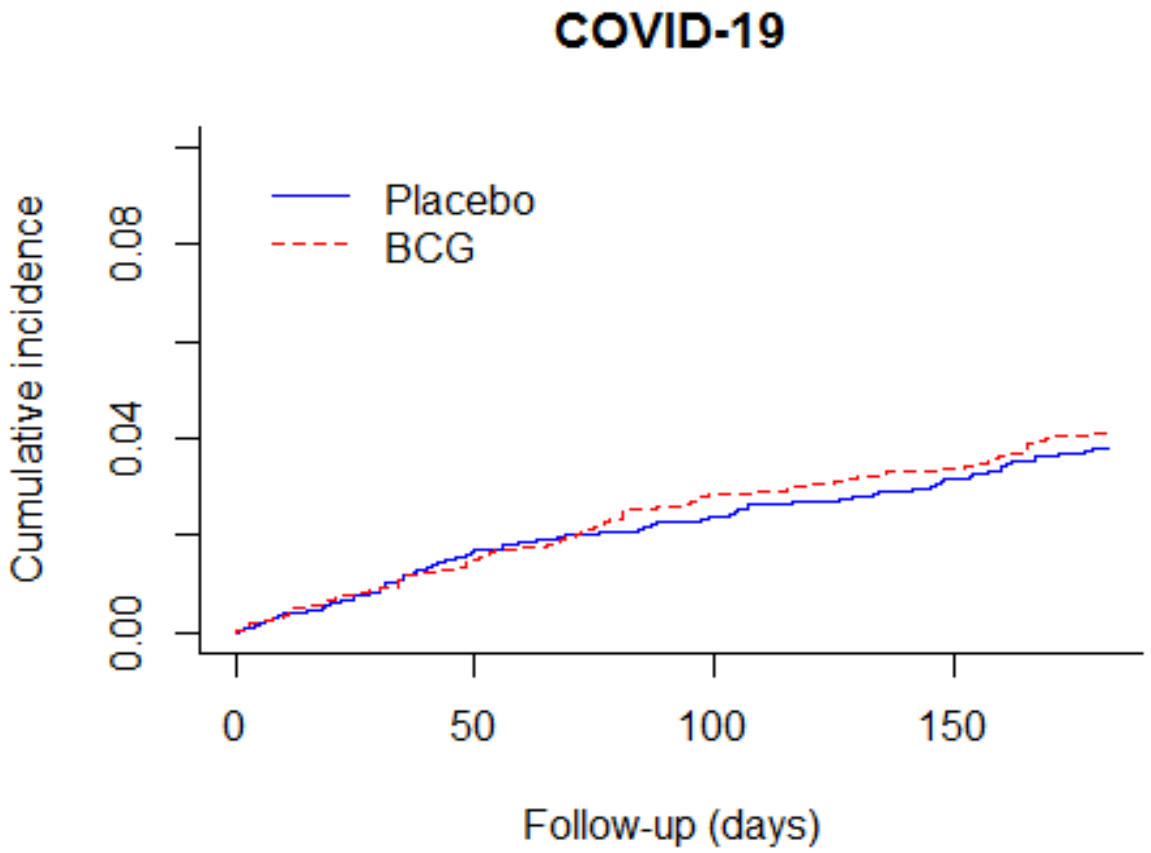
BCG-Prime study in the Netherlands (n=3000+3000)



Similar data in studies from South Africa and Denmark

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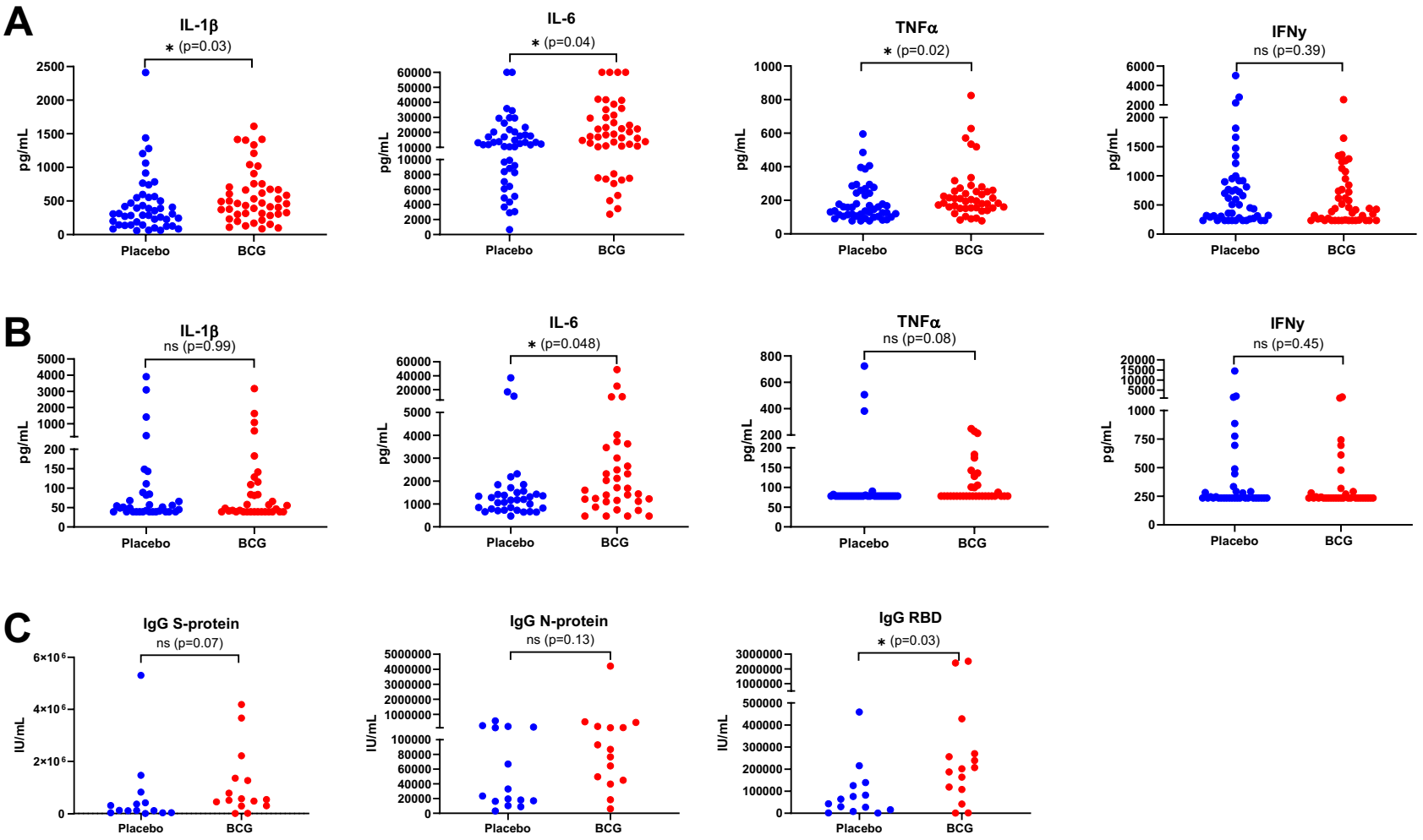
BCG-Elderly study in the Netherlands



Moorlag et al, Clin Infect Dis 2022

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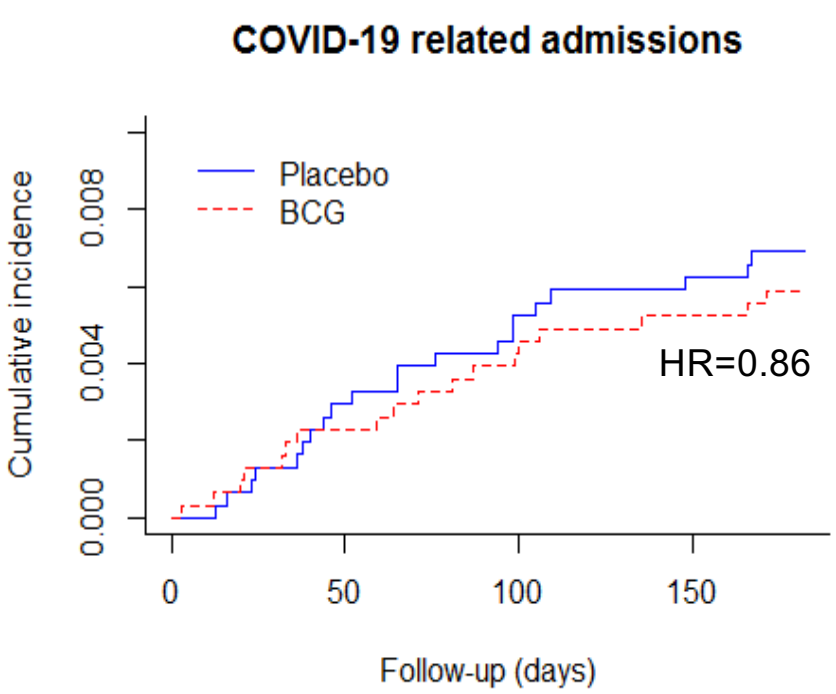

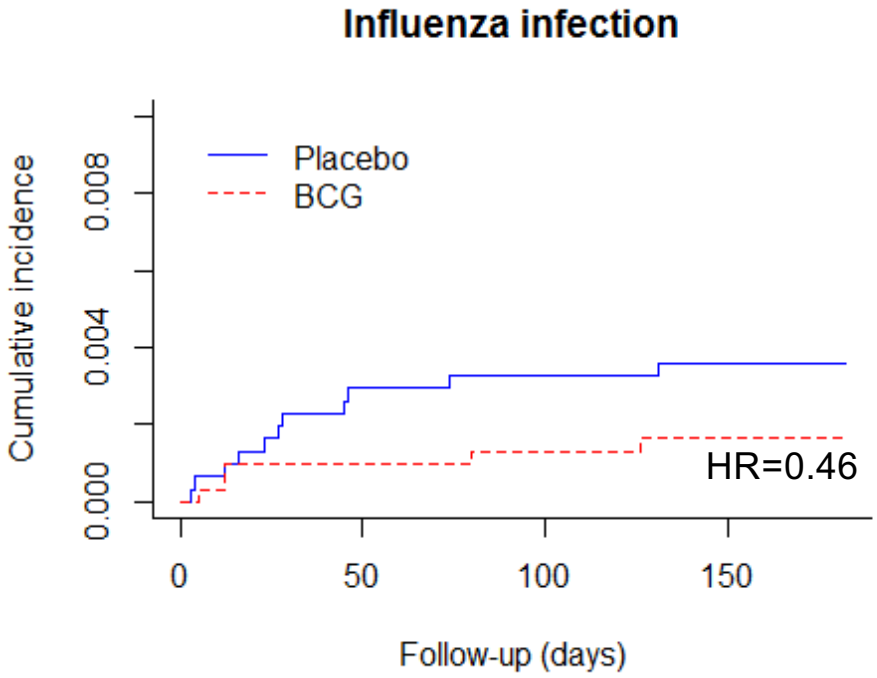

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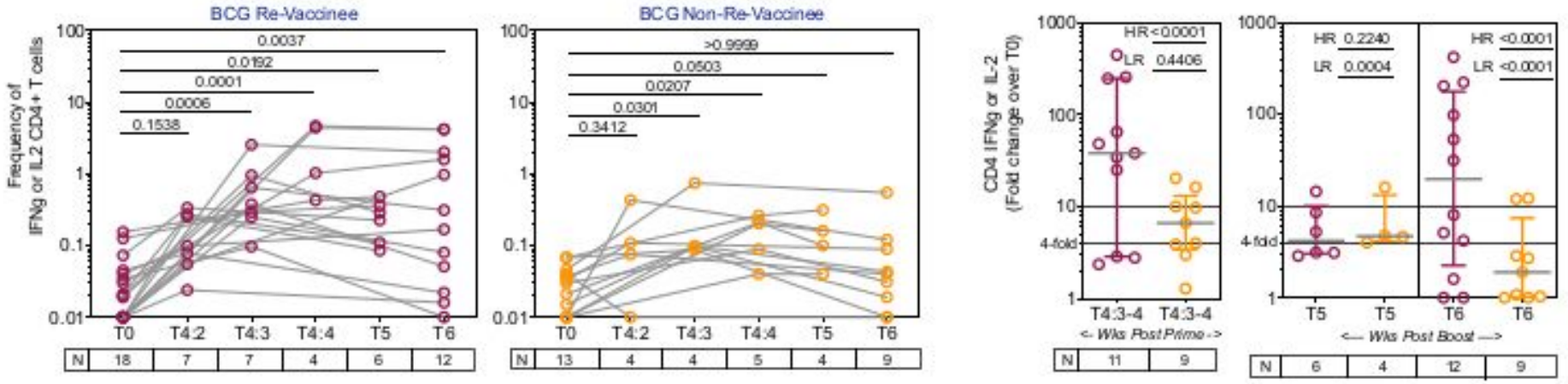
BCG revaccination qualitatively and quantitatively enhances SARS-CoV-2 spike-specific neutralizing antibody and T cell responses induced by the COVISHIELD^{TM} vaccine in SARS-CoV-2 seronegative young Indian adults



Rakshit et al, Frontiers Immunol 2022

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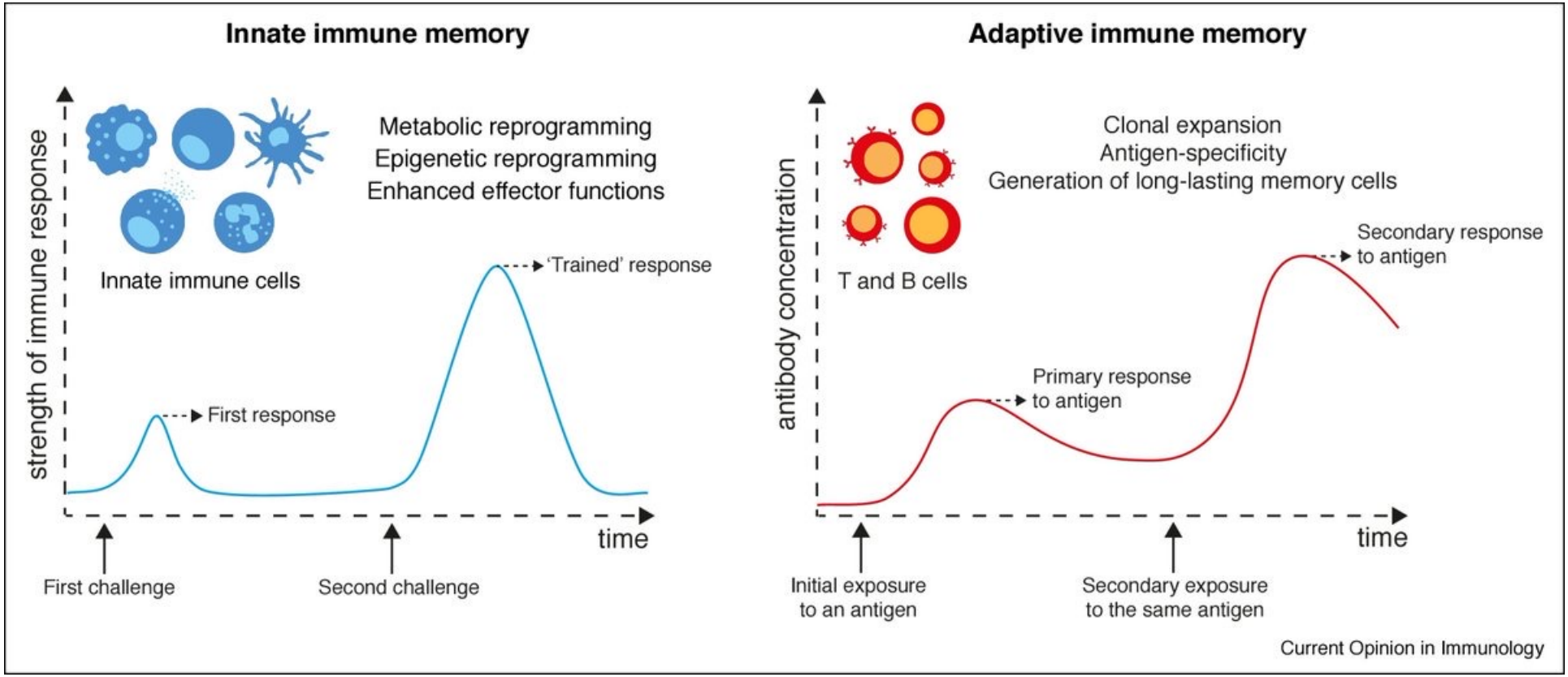
Why not build a future vaccine which combines trained immunity and adaptive memory



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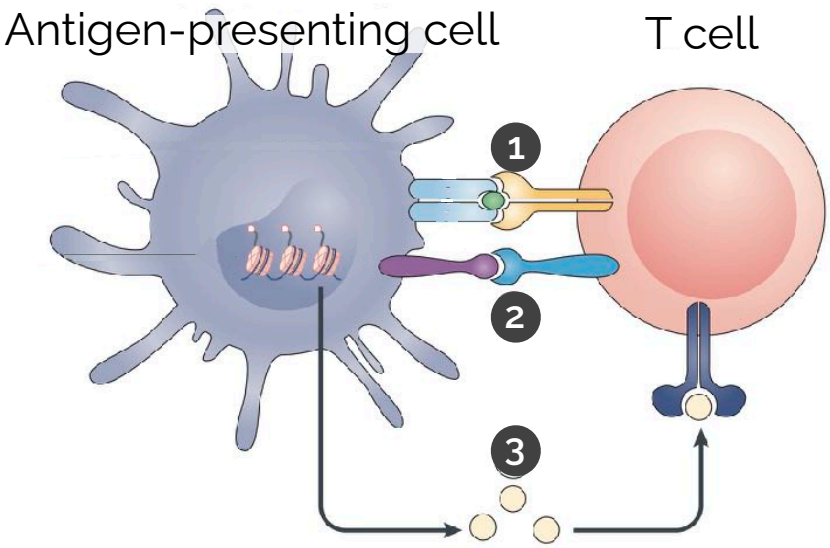
How do vaccines work?

Immune activation



Vaccine

1. Antigen
2. Adjuvants
+
3. 

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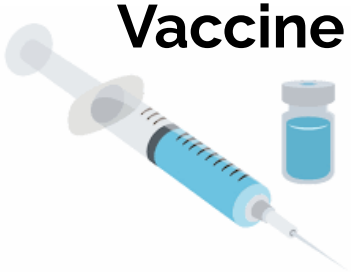
Now let's design a modular trained immunity vaccine

2 Trained immunity-inducing ligands

1 Antigens

Vaccine



1 Antigen

2 Adjuvants

\+

3

Trained immunity

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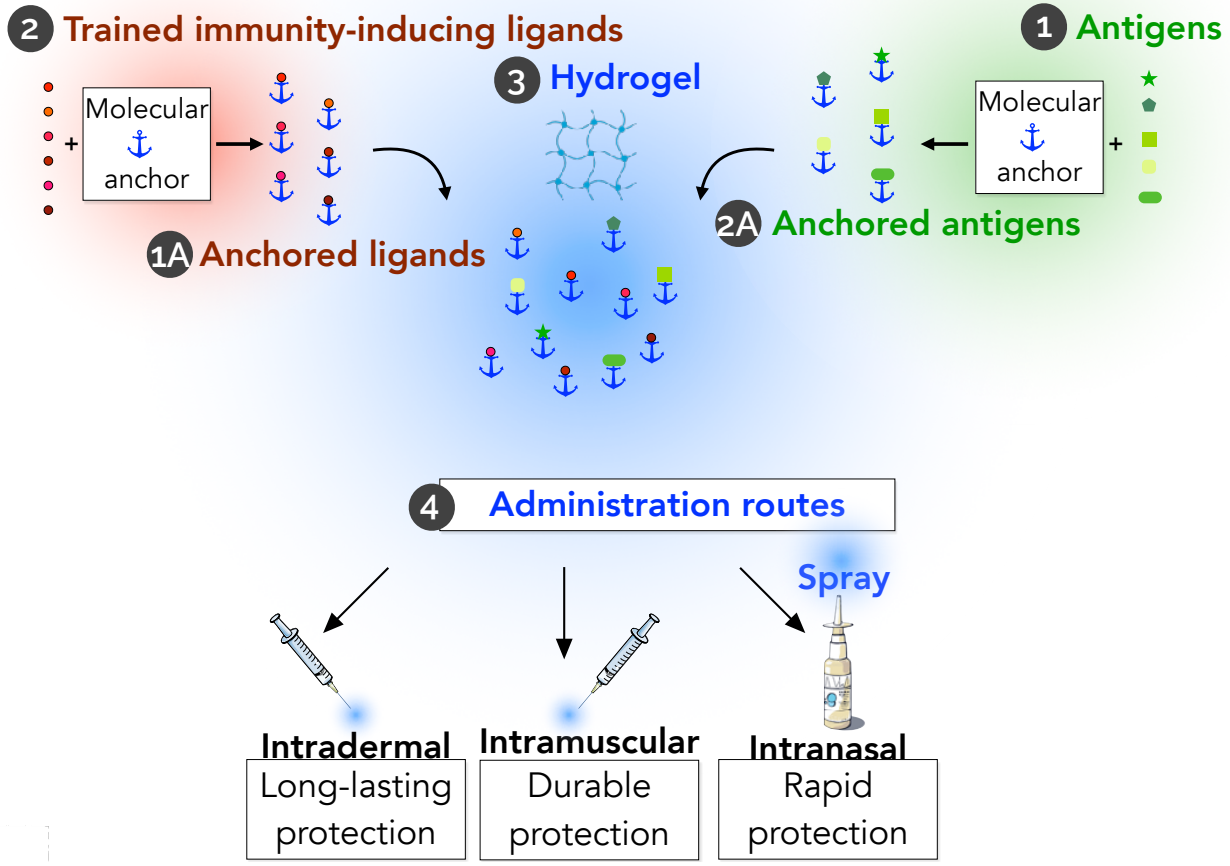
Now let's design a modular trained immunity vaccine



Providing broad protection for the elderly and vulnerable

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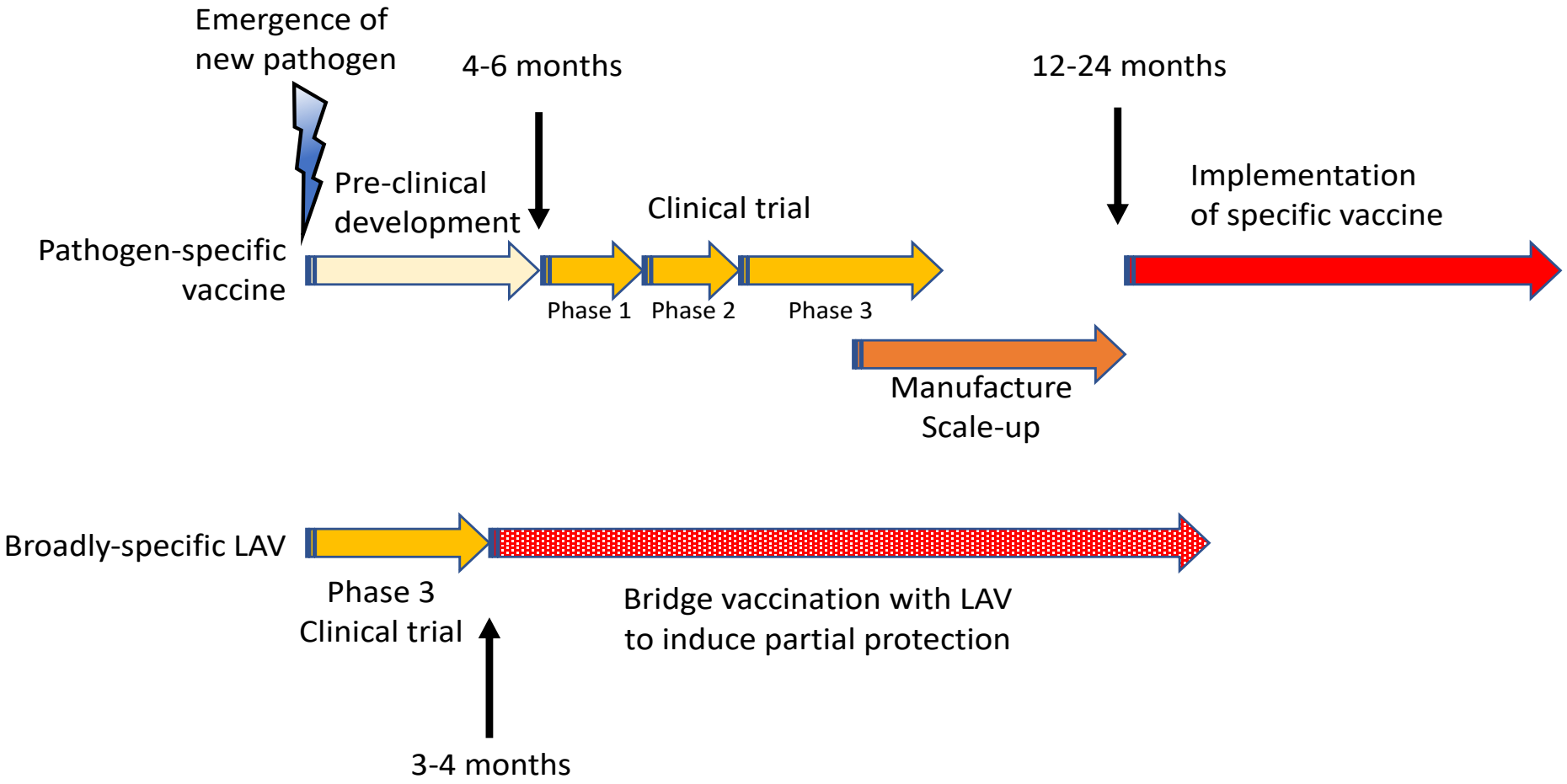
Trained immunity-inducing vaccines as a tool



Chumakov et al, PNAS 2021

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Thank you !

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