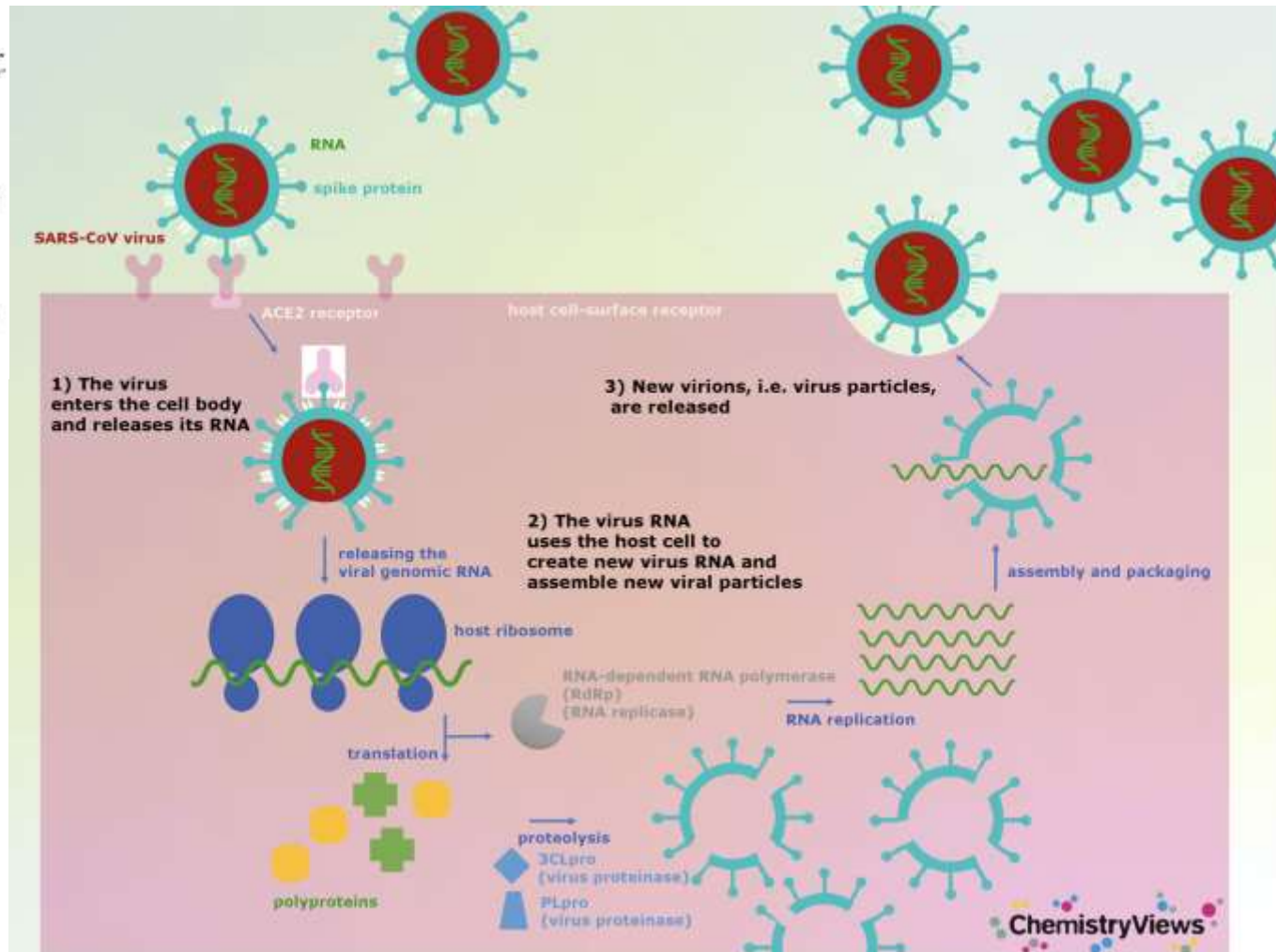
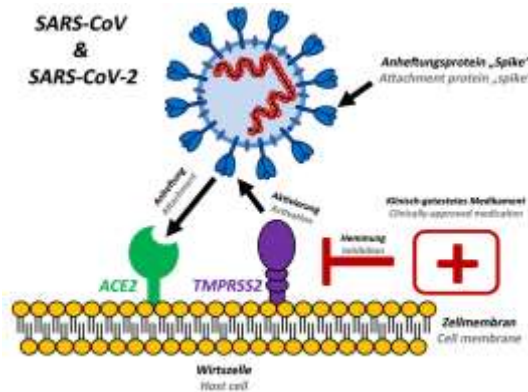


Innate immune responses in COVID-19: relevance for vaccination

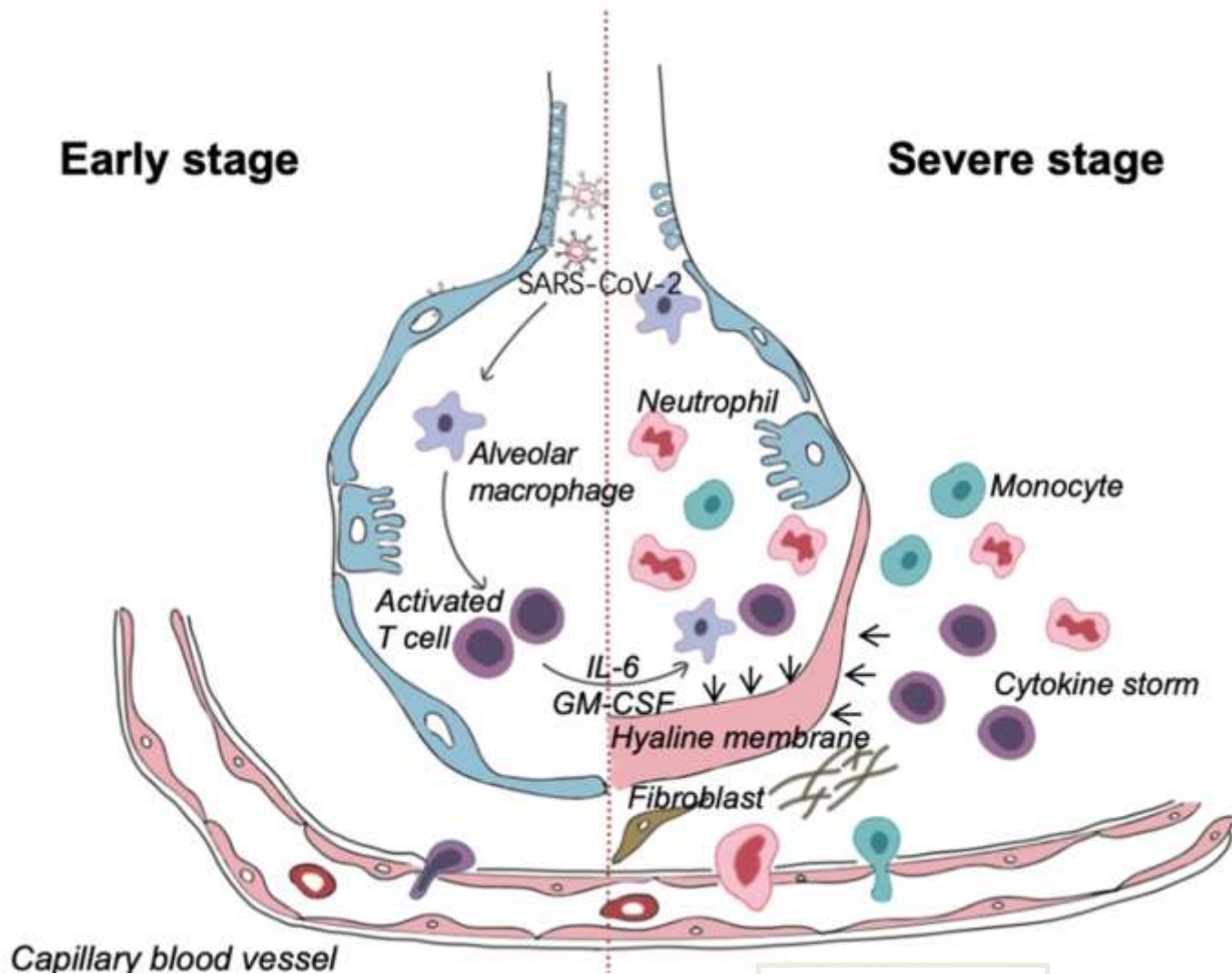
Mihai G. Netea

Radboudumc

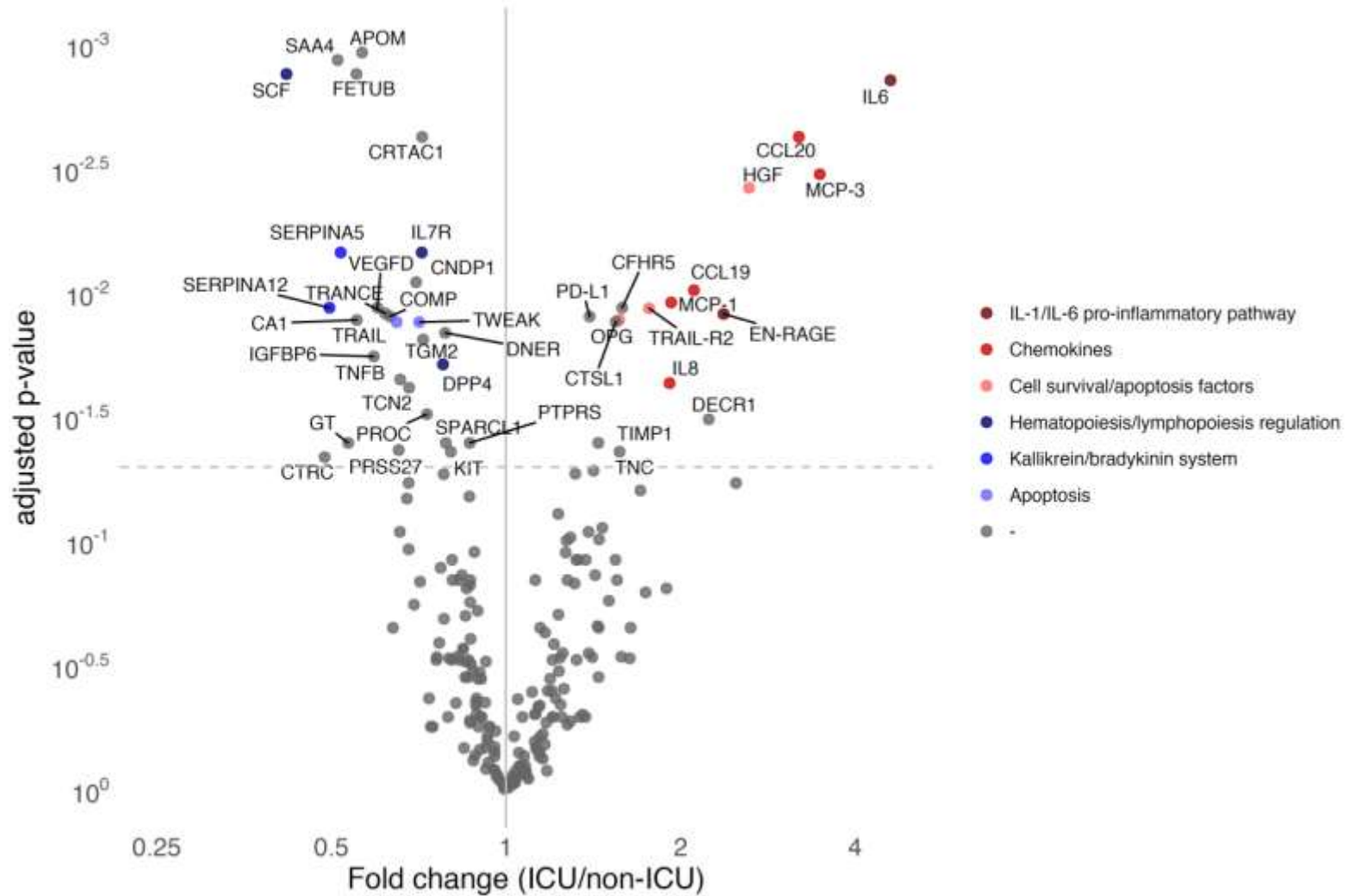
Cellular invasion by SARS-CoV-2



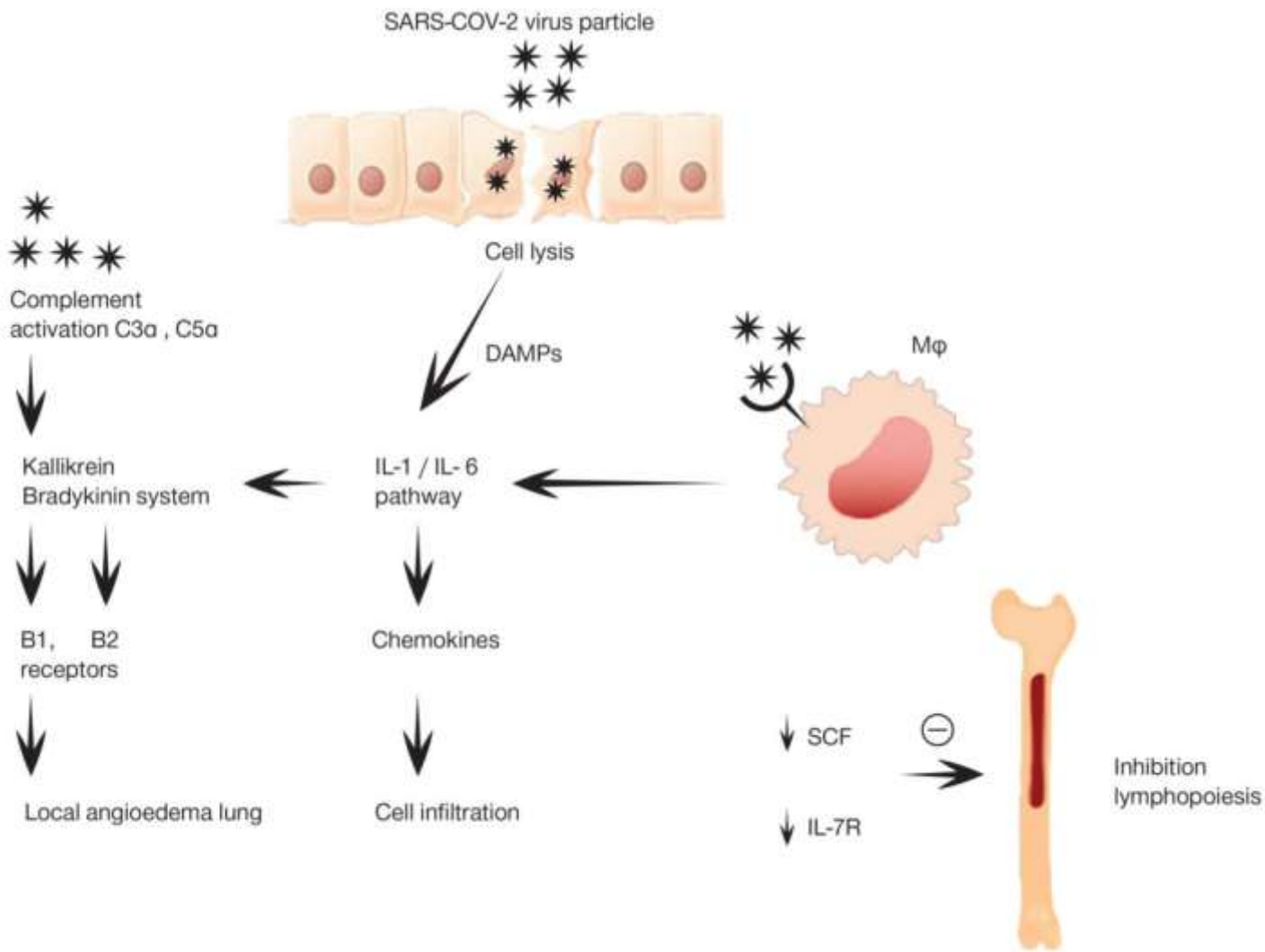
Local pathophysiology of COVID-19



Inflammatory dysregulation in COVID-19

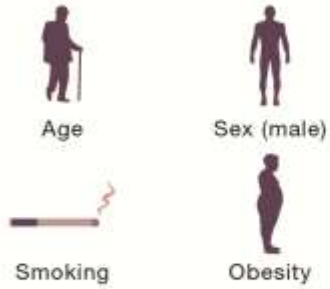


Relative homogeneity of inflammatory phenotype: clustering based on severity

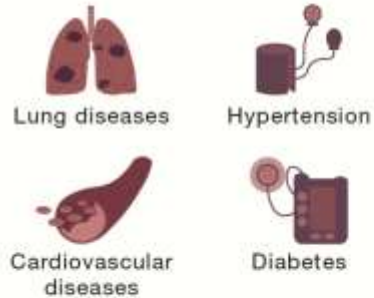


Trained immunity as prevention of infection

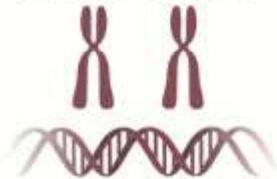
Non-genetic risk factors



Co-morbidities



Genetic factors



Early phase/prevention

High innate immune response



Low viremia



Late phase/treatment

Low symptoms
Low inflammation

Survival

Low innate immune response



High viremia



Hyperinflammation
High severity

Death



Trained immunity-based boosting



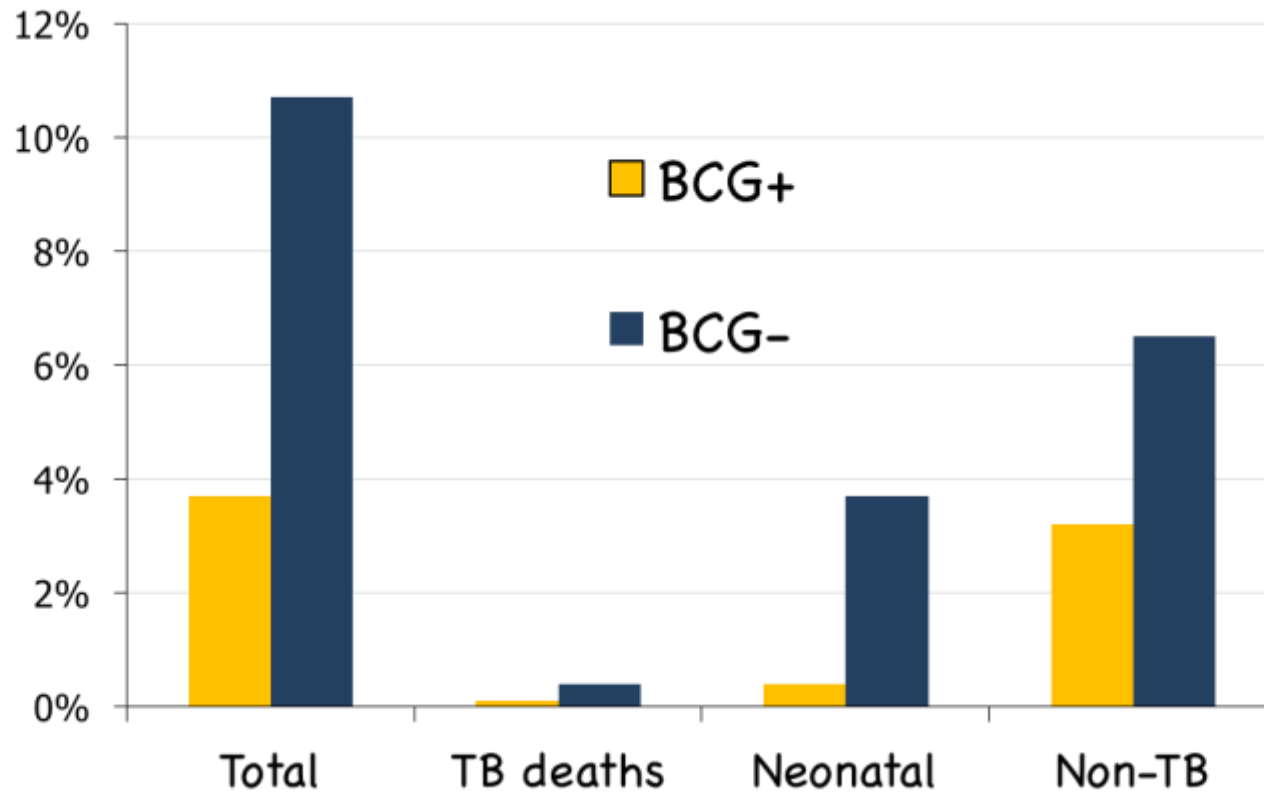
Blocking autoinflammatory loop (anti-IL-1/6)

Introducing BCG in Norrbotten, Sweden, 1927-31: Mortality at 0-4 years - 20,000 children

Coverage
highest
in families
with TB

*Reduction was
in infancy, but
TB deaths
occur later*

*This made
little sense*

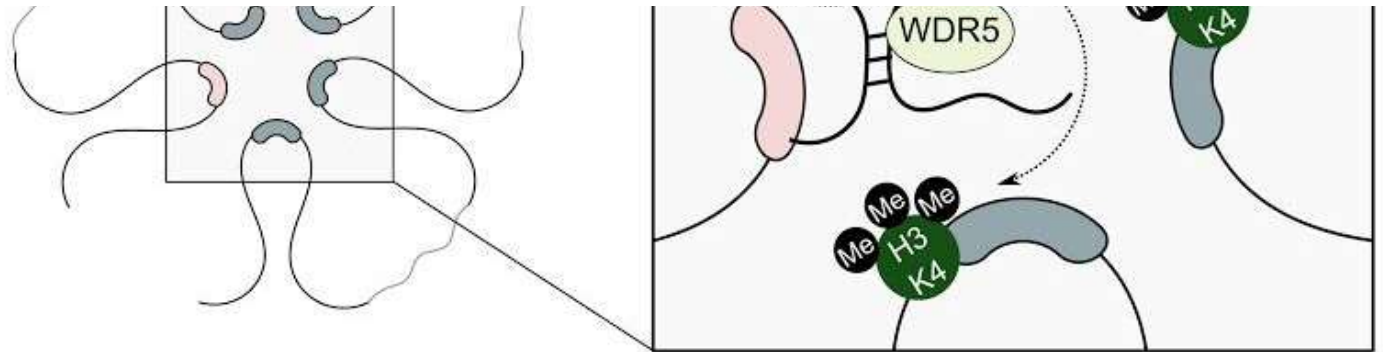


“One could evidently be tempted to find an explanation for this much lower mortality among vaccinated children in the idea that BCG provokes *a non-specific immunity...*”

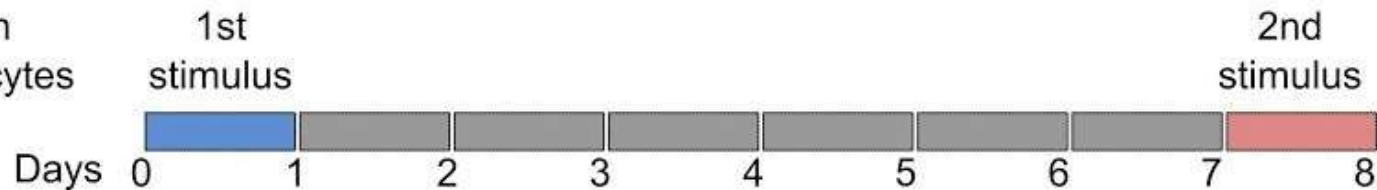
Carl Naeslund 1932

Long-term epigenetic reprogramming in myeloid cells

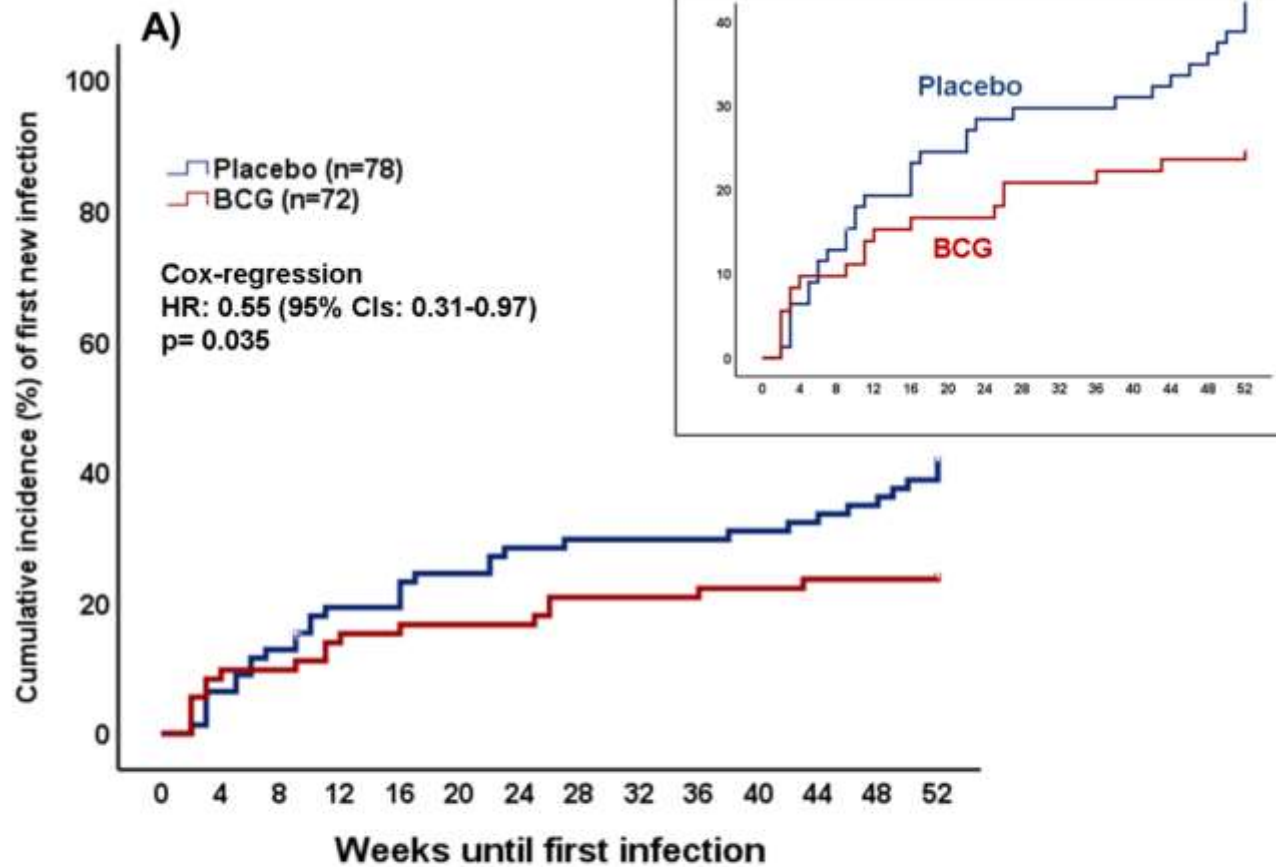
domain
(TAD)



Human
monocytes



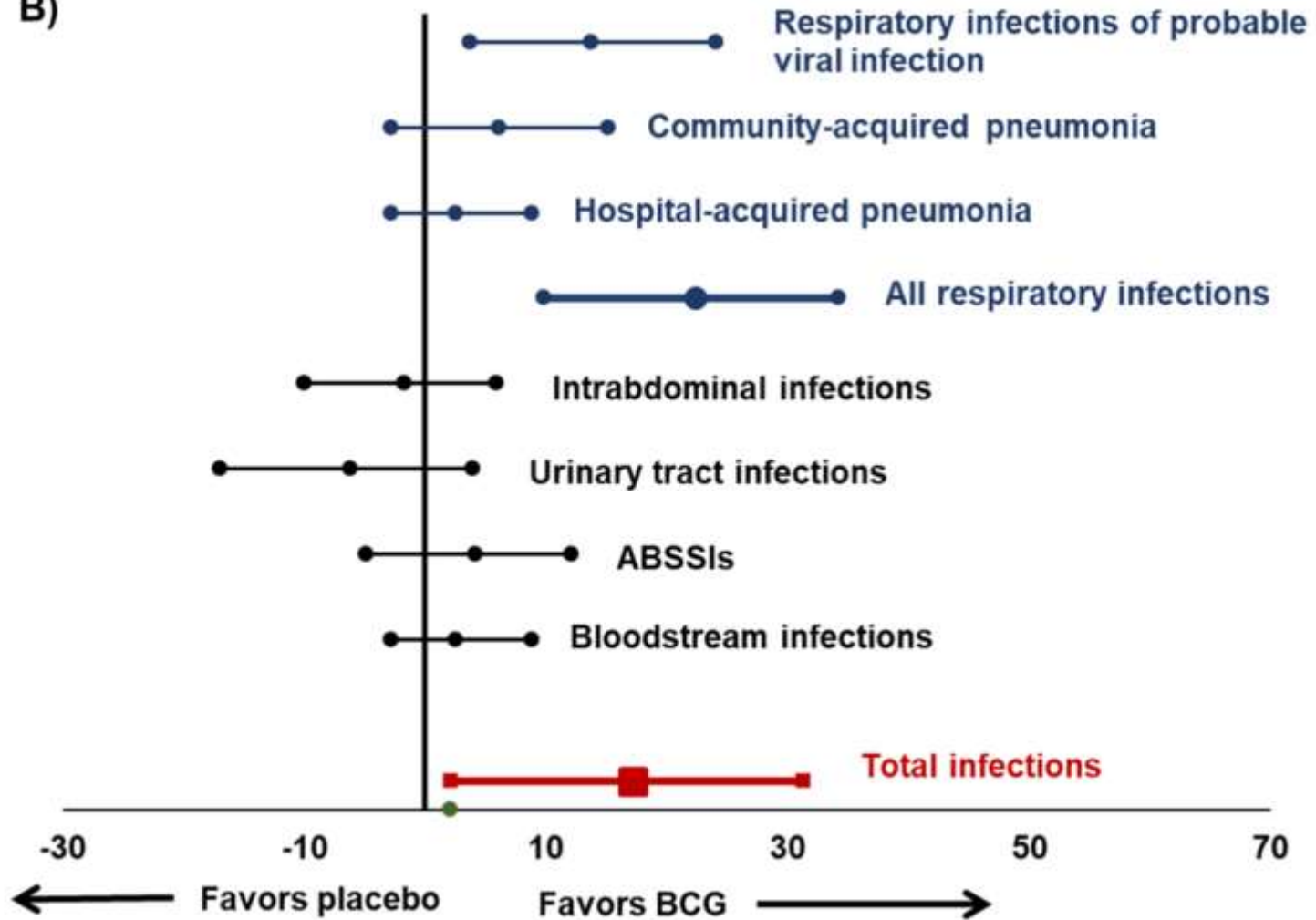
ACTIVATE study: BCG in elderly



No of pts <u>at risk</u>	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

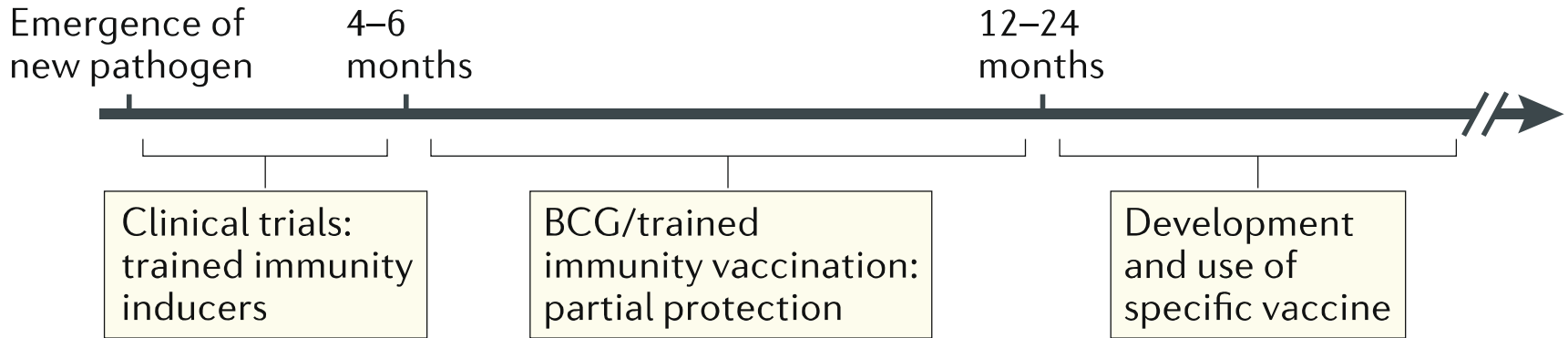
ACTIVATE study: BCG in elderly

B)



% difference with 95% CI of events between placebo and BCG

Trained immunity as a tool against a pandemic



Current randomized trials:

- 15 BCG vaccine trials
- 2 OPV trials
- 2 MMR trials

Thank you !

Department of Internal Medicine - RadboudUMC

Jorge Dominguez

Simone Moorlag

Rob Arts

Bas Blok

Charlotte de Bree

James Cheng

Siroon Bekkering

Jos W.M. van der Meer

Niels Riksen

Reinout van Crevel

Leo Joosten

Dept. Molecular Biology – Radboud University

Boris Novakovic

Sadia Saeed

Joost Martens

Colin Logie

Henk Stunnenberg

Dresden University

Ioannis Mitroulis

Triantafyllos Chavakis

Bonn University - LIMES

Katarzyna Placek

Anette Christ

Eicke Latz

Andreas Schlitzer

Joachim Schultze

Harvard University

Ramnik Xavier

University of Minho, Braga

Agostinho Carvalho

Ricardo Silvestre

Fernando Rodrigues

University of Melbourne

Nicole Messina

Nigel Curtis

Athens University

Evangelos Giamarellos

East Tennessee State University

David Williams