

Report from Workshop on Ageing and Immunity

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Initiative for Vaccine Research



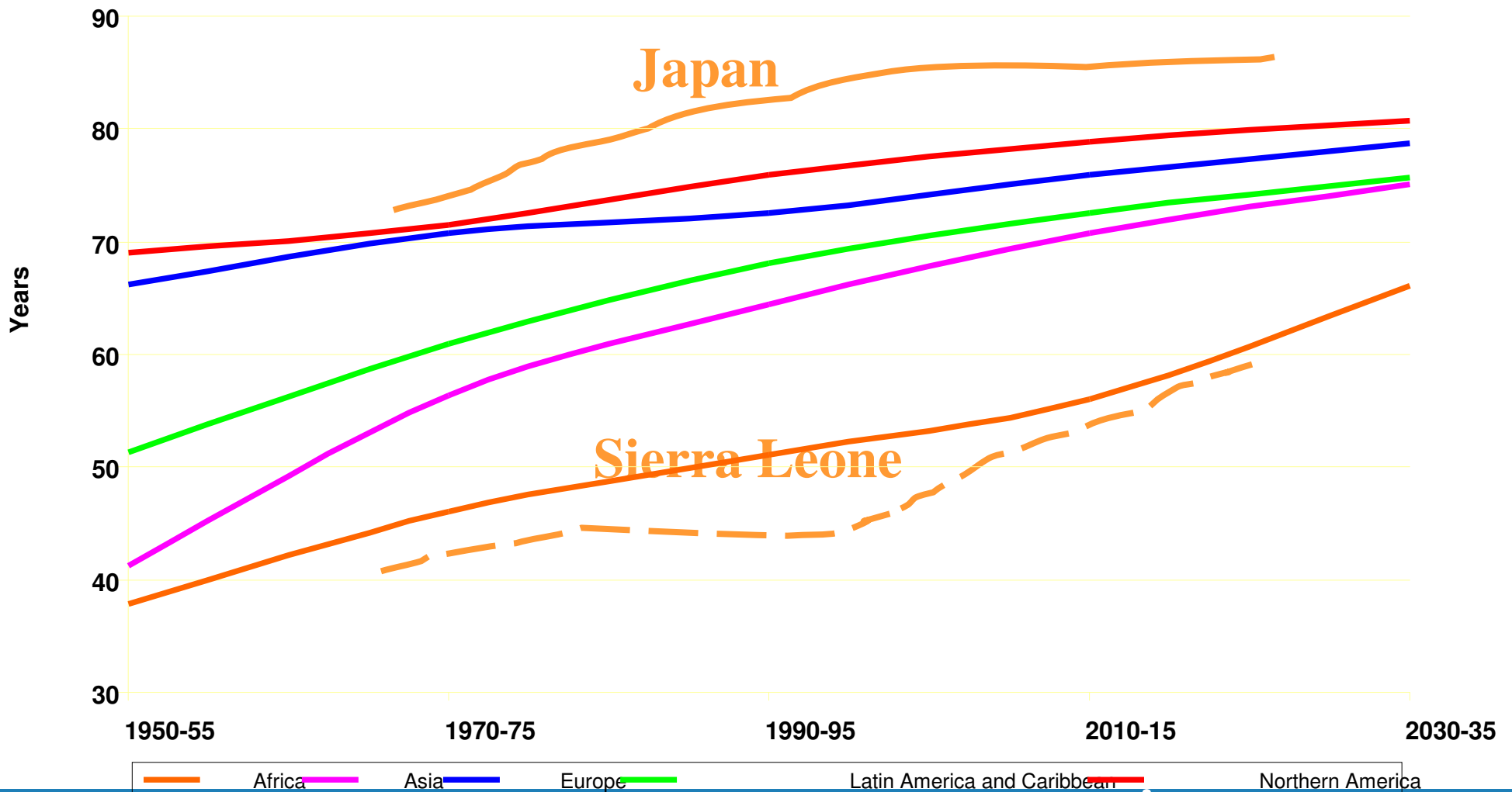
**World Health
Organization**

The population in developing countries is fast increasing - particularly the aged

Population (in billion)	2000	2025	2050
Total	6.0	7.8	8.9
More developed countries	1.2	1.2	1.2
Less developed countries	4.7	6.6	7.8
60+	0.6	1.2	2.0
More developed countries	0.2	0.3	0.3
Less developed countries	0.4	0.9	1.7

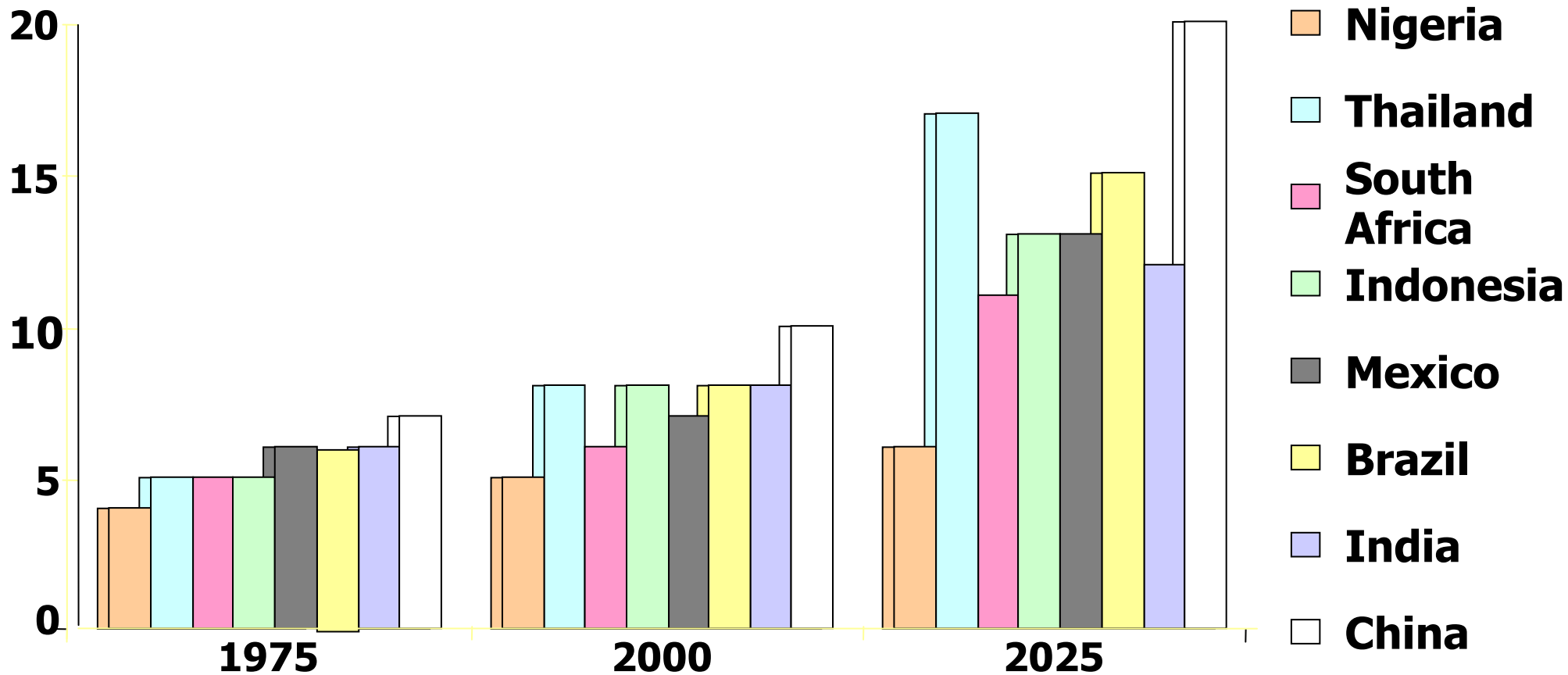


Life expectancy at birth is increasing in all regions



Population 60 years and over as Percentage of total Population is increasing all regions

Percentage of total population



And everywhere the final years are spent in poor health

YEARS IN POOR HEALTH

Life Expectancy at Birth minus Healthy Life Expectancy at Birth

Countries	Males	Females
Brazil	9	11
Canada	8	8
China	7	8
Congo	8	8
Costa Rica	10	11
Greece	7	8
India	7	9
Jamaica	7	8
Japan	6	7

Countries	Males	Females
Lebanon	9	10
Mexico	9	9
Mozambique	8	8
Norway	7	8
Russia	5	8
Saudi Arabia	8	9
South Africa	5	5
Switzerland	7	8
USA	8	9

Source: World Health Report WHO 2004



But..

The developed world became rich
before it became old.

Developing countries are becoming
old
before they become rich.



The role of immunity in the health of elderly

- Effect of ageing on innate immunity
- Age-related changes to T- and B-cell function
- Role of chronic viral infection
- Age-related response to vaccination
- Overcoming age-related sub-optimal immunity
 - Need for CD8 response to influenza vaccine
 - ID delivery for influenza vaccine
 - Herpes zoster and boosting against chicken-pox

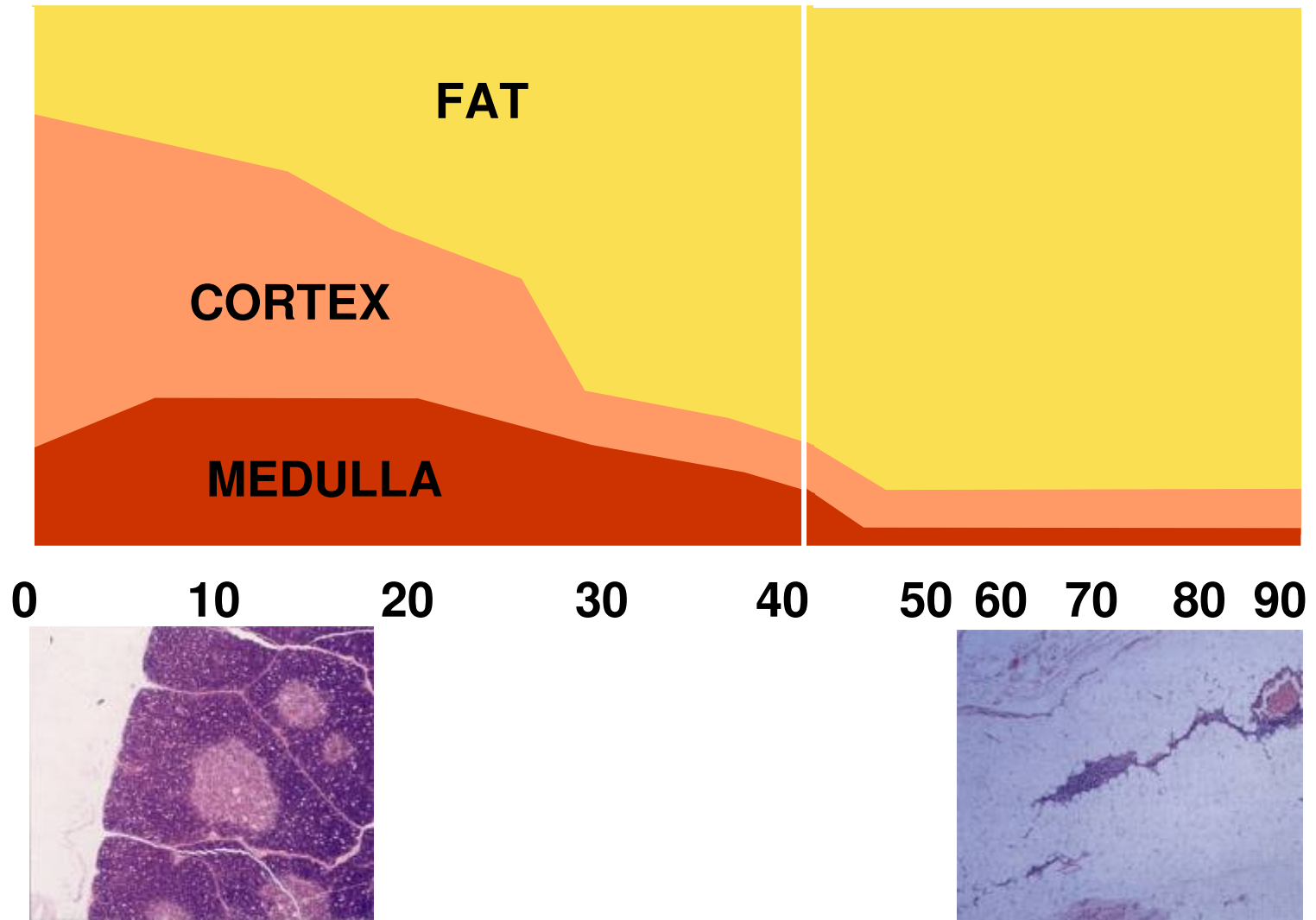


Age related impairments of antigen uptake and transport

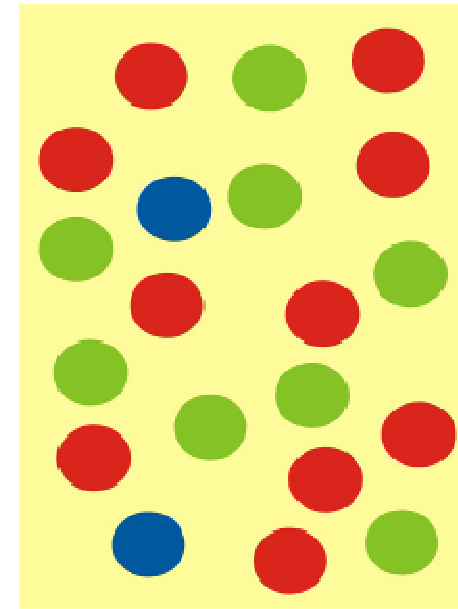
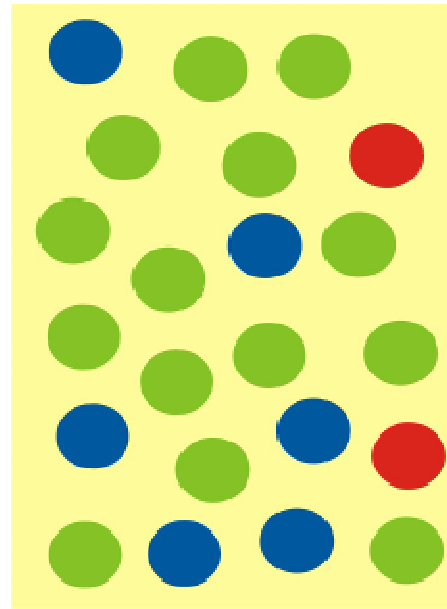
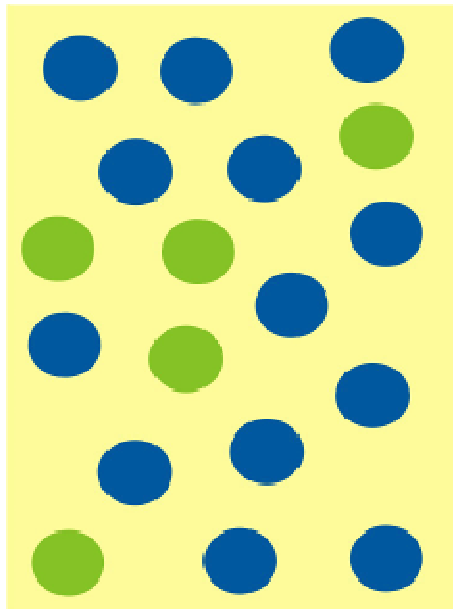
- **Due to subclinical ubiquitous inflammatory processes (“inflammaging”) the threshold for the induction of a “danger” signal to be induced by vaccine with adjuvant increases.**
- **Migration of dendritic cells to the lymph node is impaired and functional defects of antigen-presenting cells may hamper uptake and presentation of antigen.**



Progressive reduction in size due to depletion of thymic cortex and medulla



Changes in the T cell repertoire throughout life



young naïve T cell
memory T cell
effector T cell

GVRIF 2008 Paris



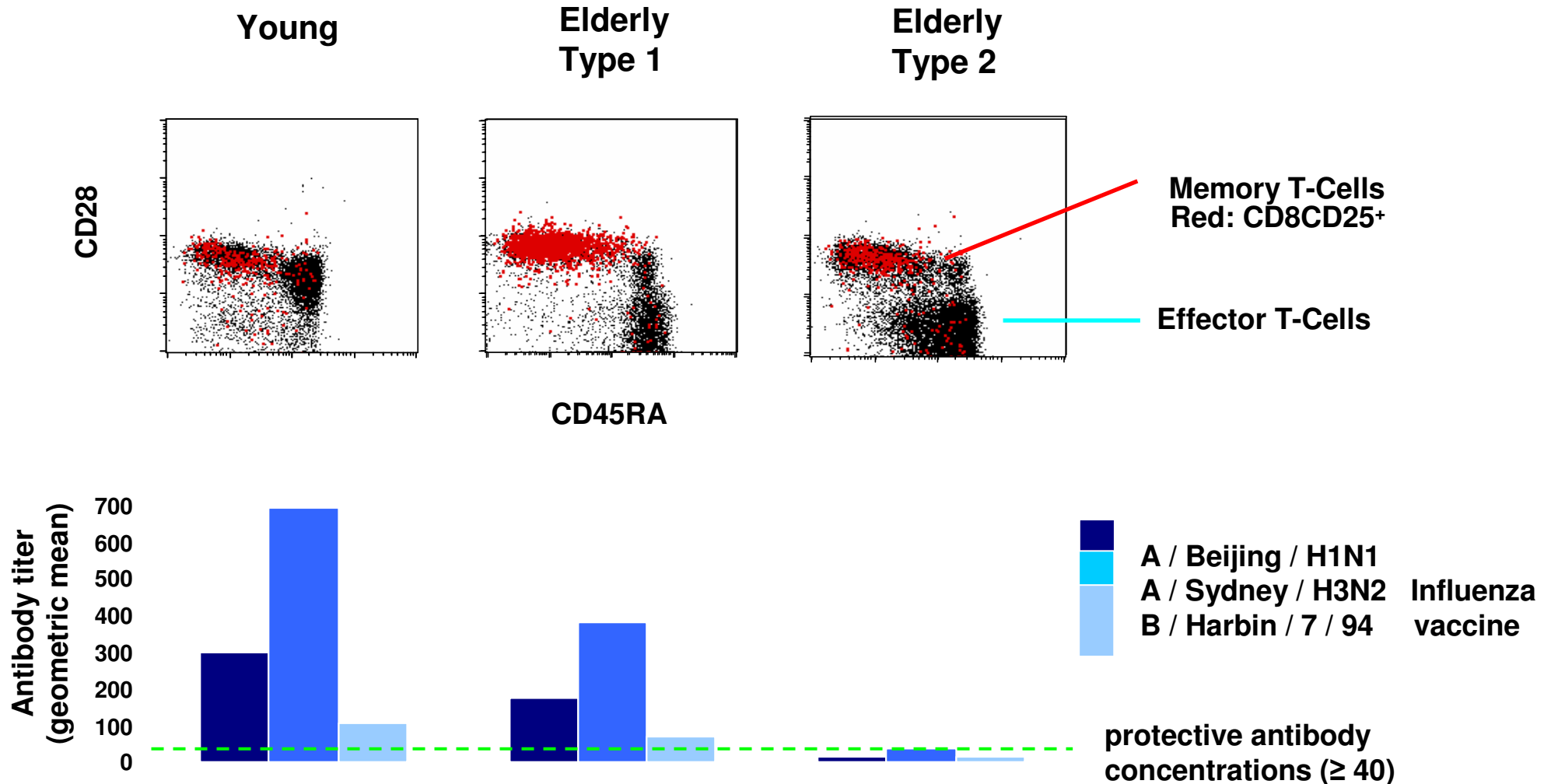
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Age-related changes of naïve T cells

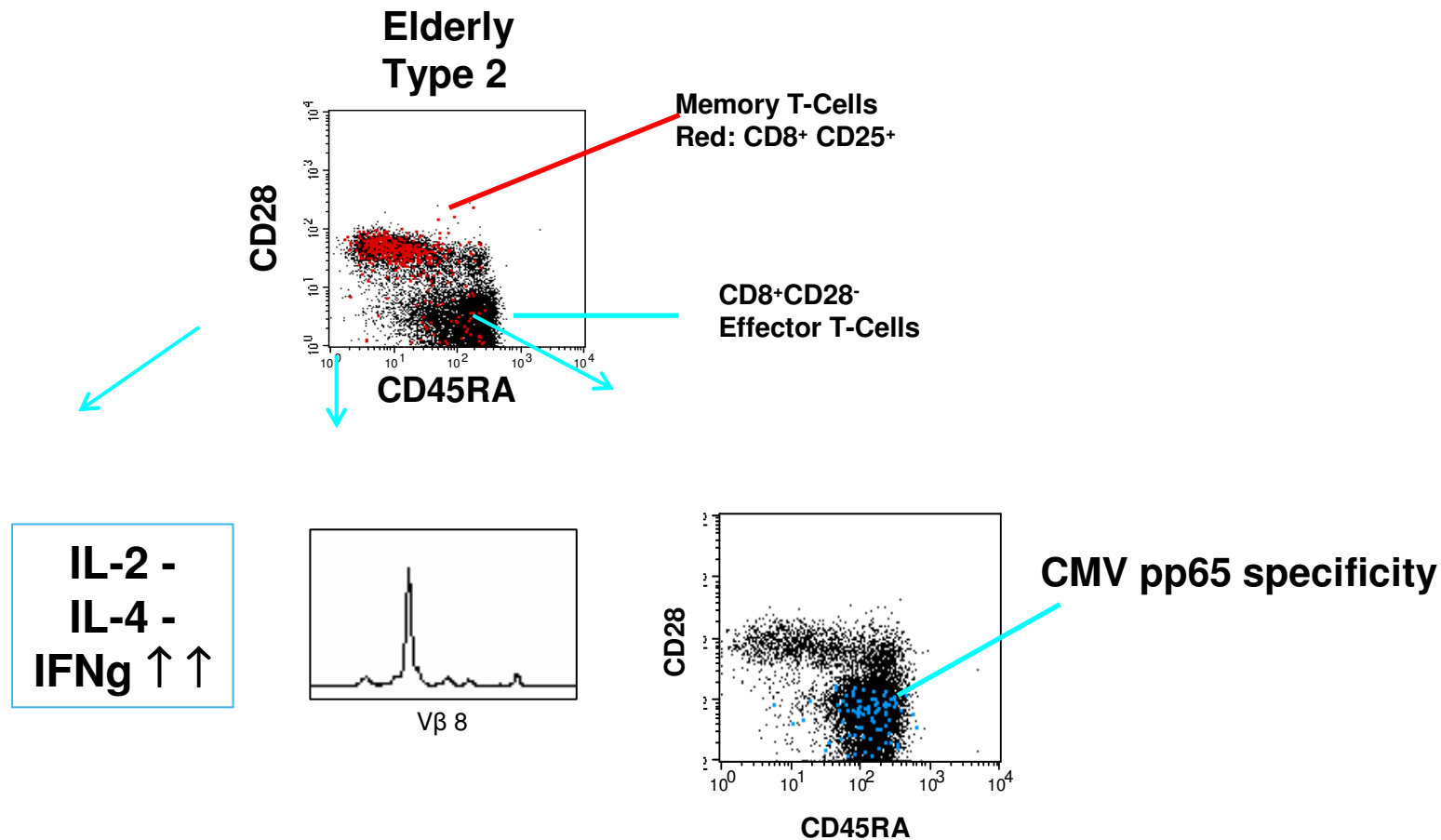
- **Due to the involution of the thymus, the naïve T cell population from elderly persons is extremely small, has a restricted diversity and shortened telomeres in comparison to young controls**
- **This may be a problem when elderly persons are exposed to neoantigens such as travel vaccines or during pandemic FLU**



Not all elderly are the same: The memory/effector CD8⁺ cell ratio varies in elderly persons



Effector CD8⁺T cells accumulate in elderly non-responders and are proinflammatory and frequently specific for CMV



Age-related impairments of memory and effector T cells

- In a subgroup of elderly persons a diverse CD8⁺CD25⁺ memory T cell population exists, which produces IL-2 and IL-4 and coincides with a good humoral response following vaccination
- Effector CD8 T cells accumulate in elderly persons which are proinflammatory and frequently specific for CMV
- The large number and proinflammatory properties of these cells may contribute to the inflammatory status of old age and inhibit antibody production



Age-related impairments in the B cell pool

generation of B cell precursors ↓

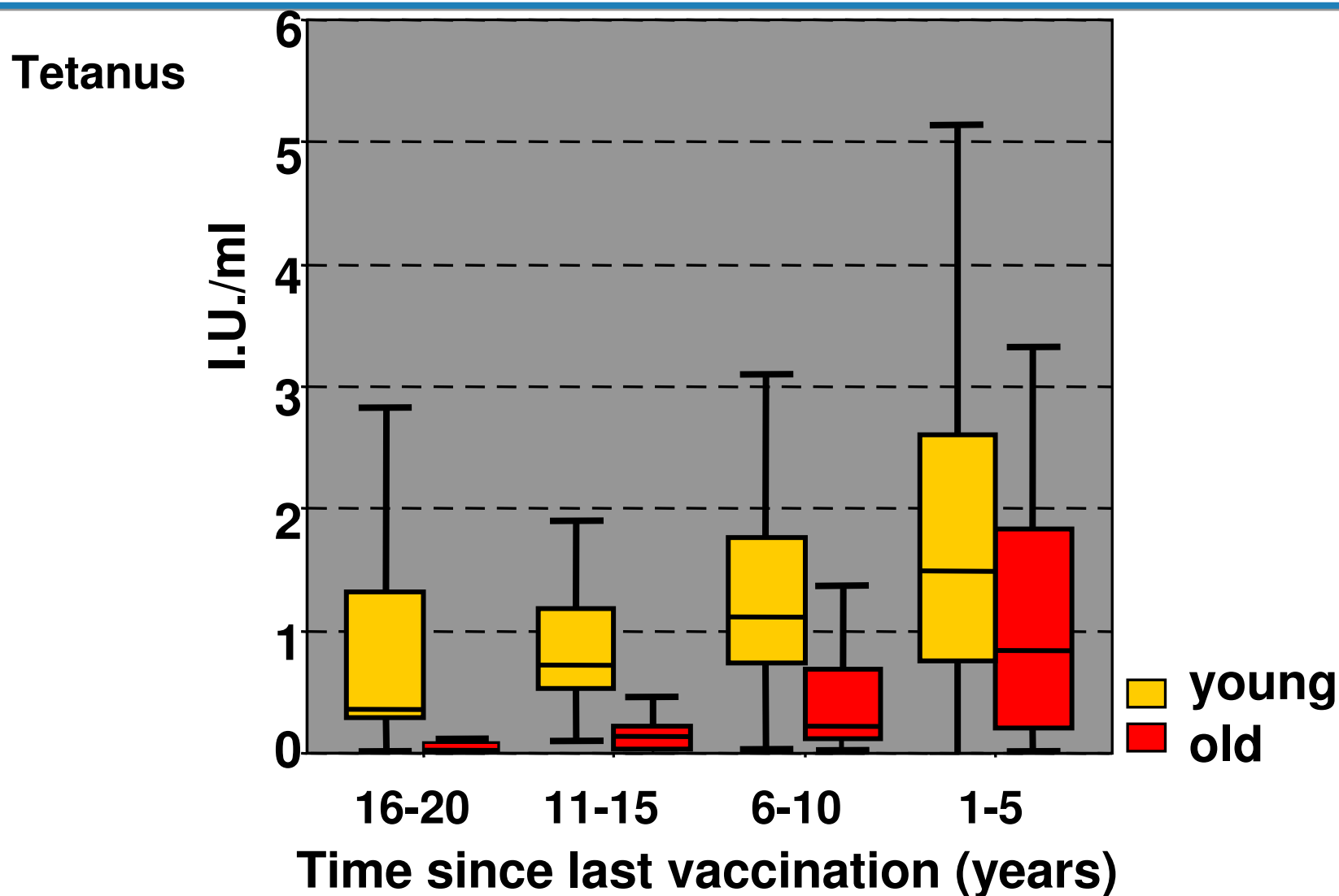
diversity of the B cell repertoire ↓

size and number of germinal centers ↓

serum antibodies specific for foreign antigens ↓

serum antibodies specific for self-antigens ↑

Antibody concentrations in young and elderly adults depending on the timepoint of the last vaccination



Difficulties in interpreting immunogerontological observations in humans

State of health between age-groups compared and between individuals within each age-group will differ (*pathology, nutrition*).

Data from **cross-sectional studies** may be comparing different young and old populations (*genetics, environment*).

Possible solutions:

Screening protocols; selection of „successfully aged“ (eg. centenarians, **SENIEUR**)

Longitudinal studies; twin studies; family studies



Which immunological parameters are important for successful ageing?

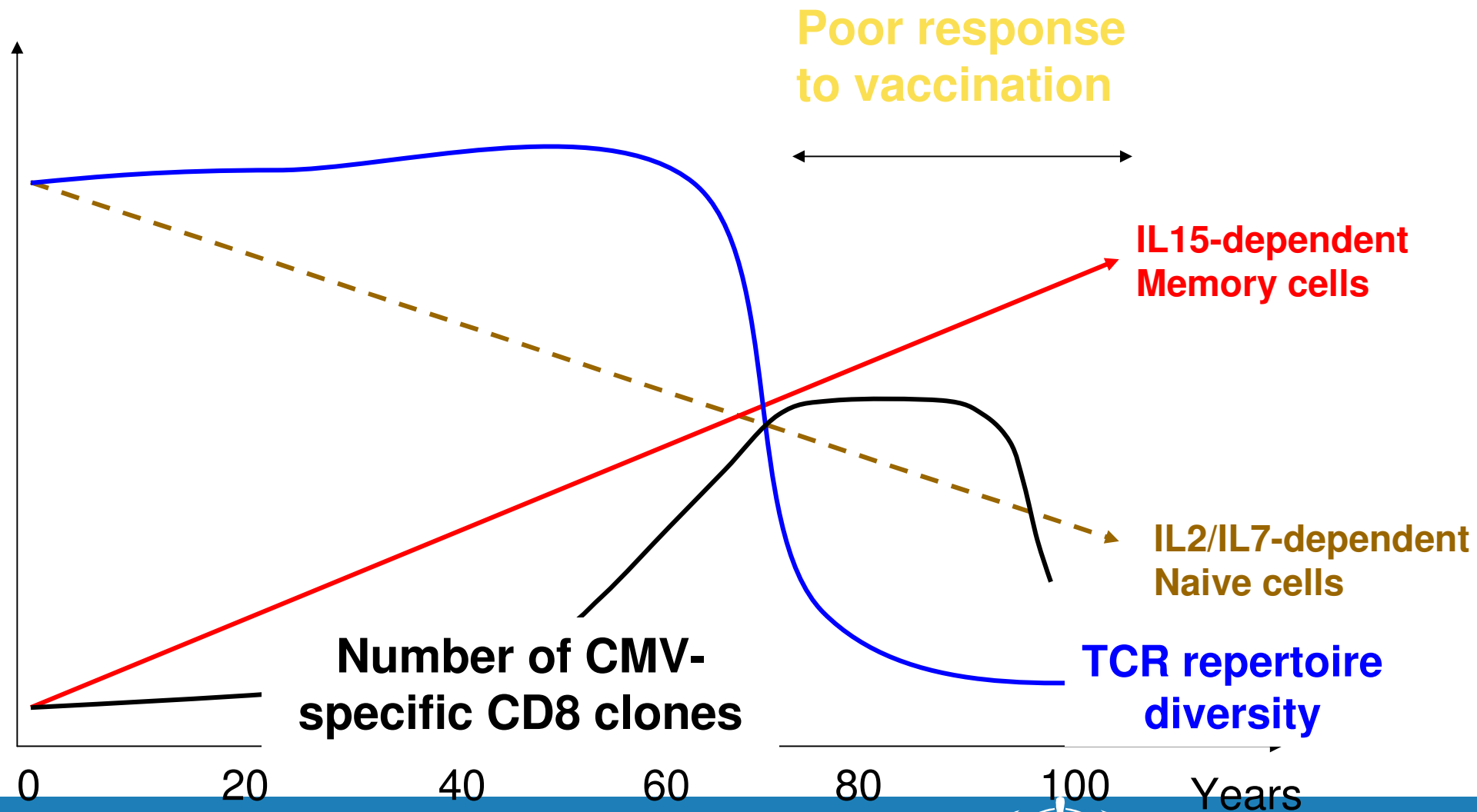
*Jönköping OCTO longitudinal studies are determining an „**immunological risk profile**“ predicting mortality in the very old*

The **IRP** is characterised by

- * CD4:8 ratio of < 1
- * poor T cell proliferative responses
- * increased CD8-positive CD28-negative cells
- * low B cells
- * **CMV-seropositivity**



Model for the evolution of T cell immunity over the lifespan

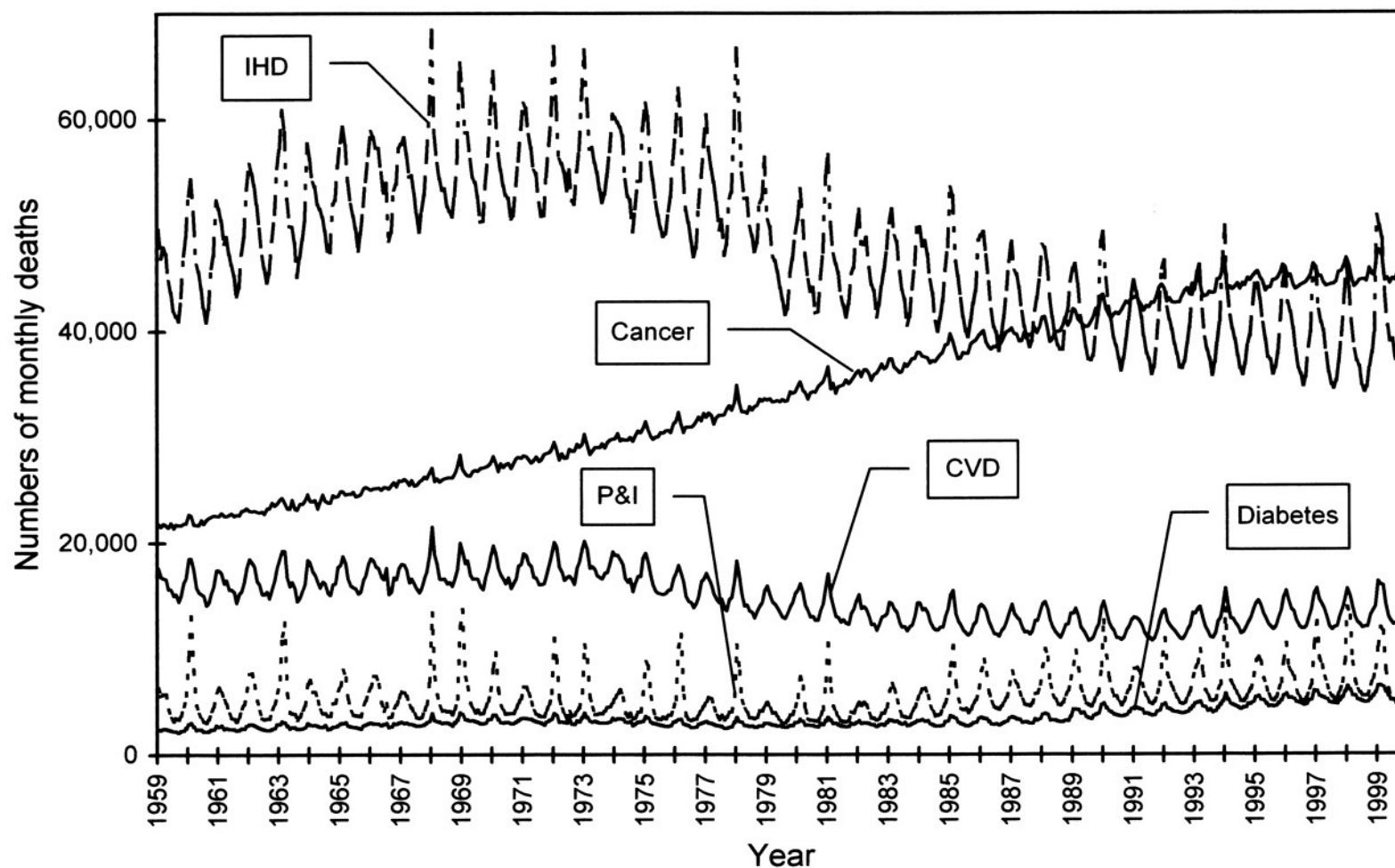


Conclusions

- T cell immunosenescence does contribute materially to morbidity and mortality in the very elderly
- Immune risk profiling predicts mortality
- CMV accelerates T cell immunosenescence
- Sequential recruitment, expansion and loss of CMV-specific T cell clones suggests a contribution of failing CMV-immunosurveillance to mortality in the very elderly – at least in Sweden



Influenza: predictor of excess mortality

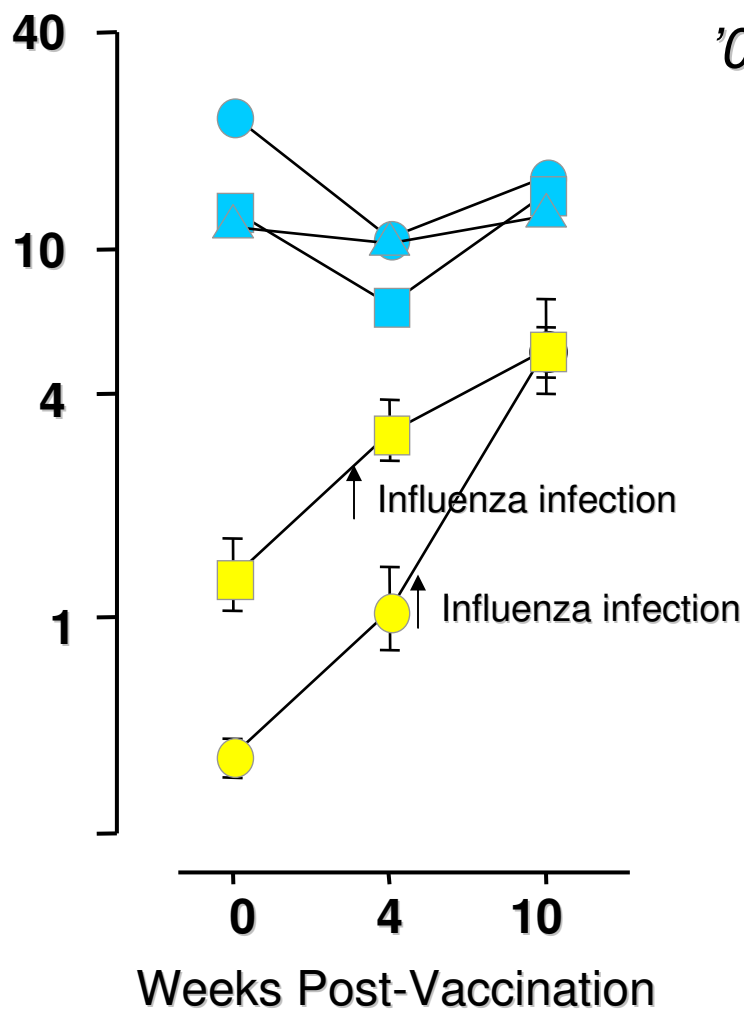


IFN- γ : IL10 ratio

Effect of Influenza Vaccination and Infection

- ▲— Young, flu-
- Old, flu-
- CHF, flu-
- Old, flu+
- CHF, flu+

Geometric Mean
IFN- γ : IL-10



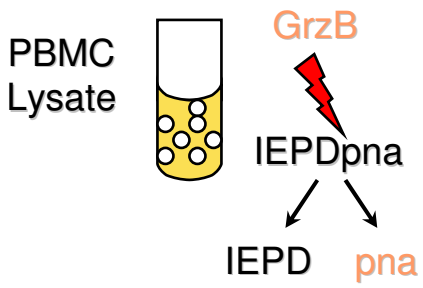
adjusted for ACEI, statin, SMWT
Pan: Flu vs. No Flu, P < .0001
error bar: std dev



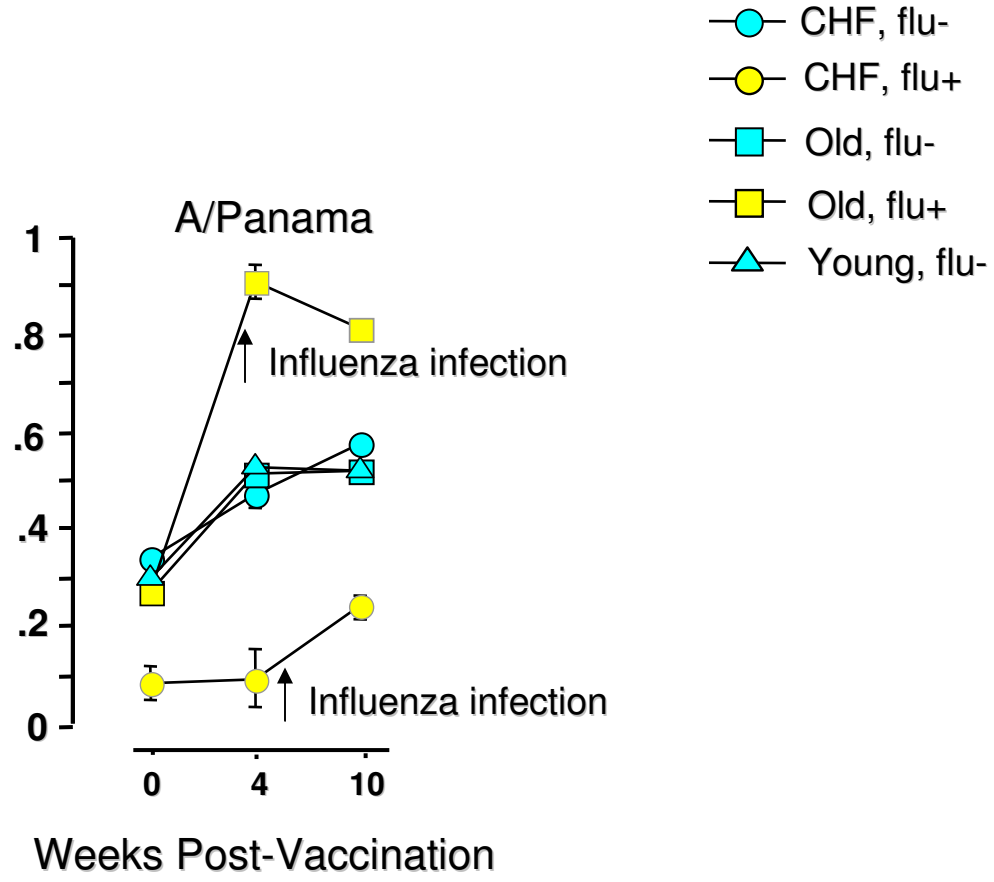
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Granzyme B Level:

Effect of Influenza Vaccination and Infection



Mean Log Grz B
U/mg protein



adjusted for ACE, statin, SMWT
Panama: H3N2 vaccine strain
Wyoming: H3N2 circulating strain

McElhaney et al. J Immunol 176:6333-9, 2006

Influenza in the elderly

- HI antibody titers as a sole measure of vaccine efficacy may not predict protection
- Cytokine and granzyme B responses to influenza may complement antibody titers in the evaluation of vaccine efficacy
- There remains a significant margin for improvement of both pandemic and seasonal influenza vaccines - the aging immune system may senesce but memory is not lost!
 - In in-vitro studies some adjuvants such as polyI:C are able to restore effector function.

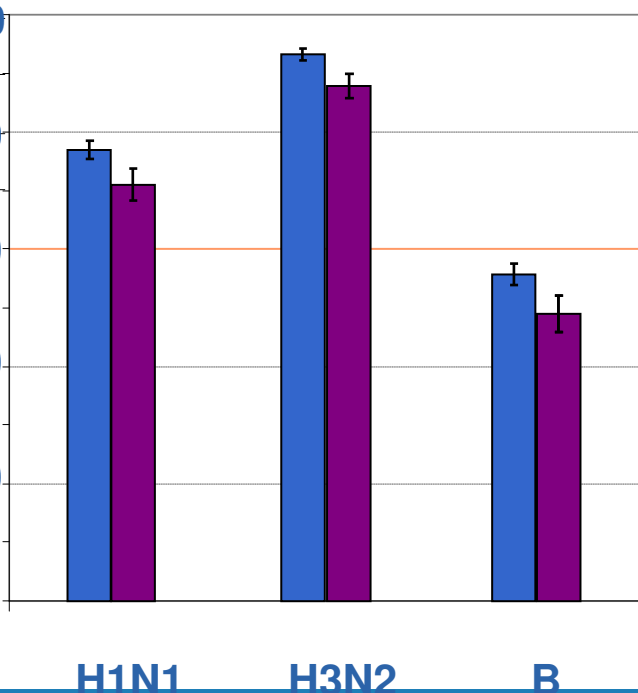


Intradermal delivery of influenza vaccine in elderly

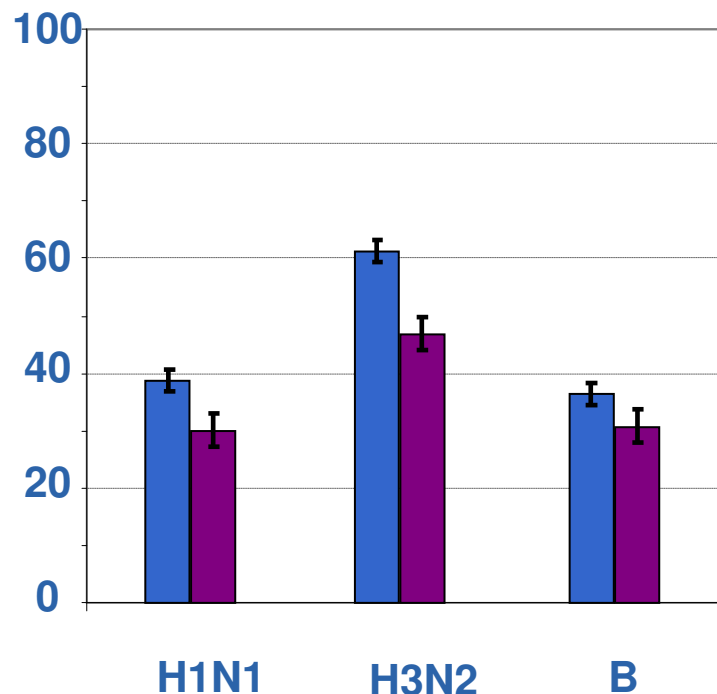
Phase 3 Superiority testing 15µg ID vs 15µg IM

- Criterion for superiority met: seroprotection rates were significantly higher with ID vaccine against all strains
- EMA criteria: immune responses significantly higher with ID for all strains and criteria

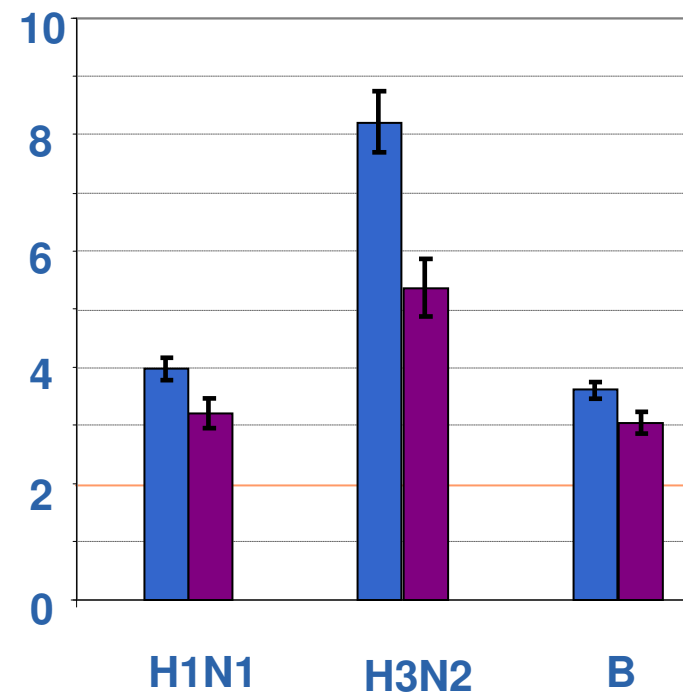
Seroprotection rate (%)



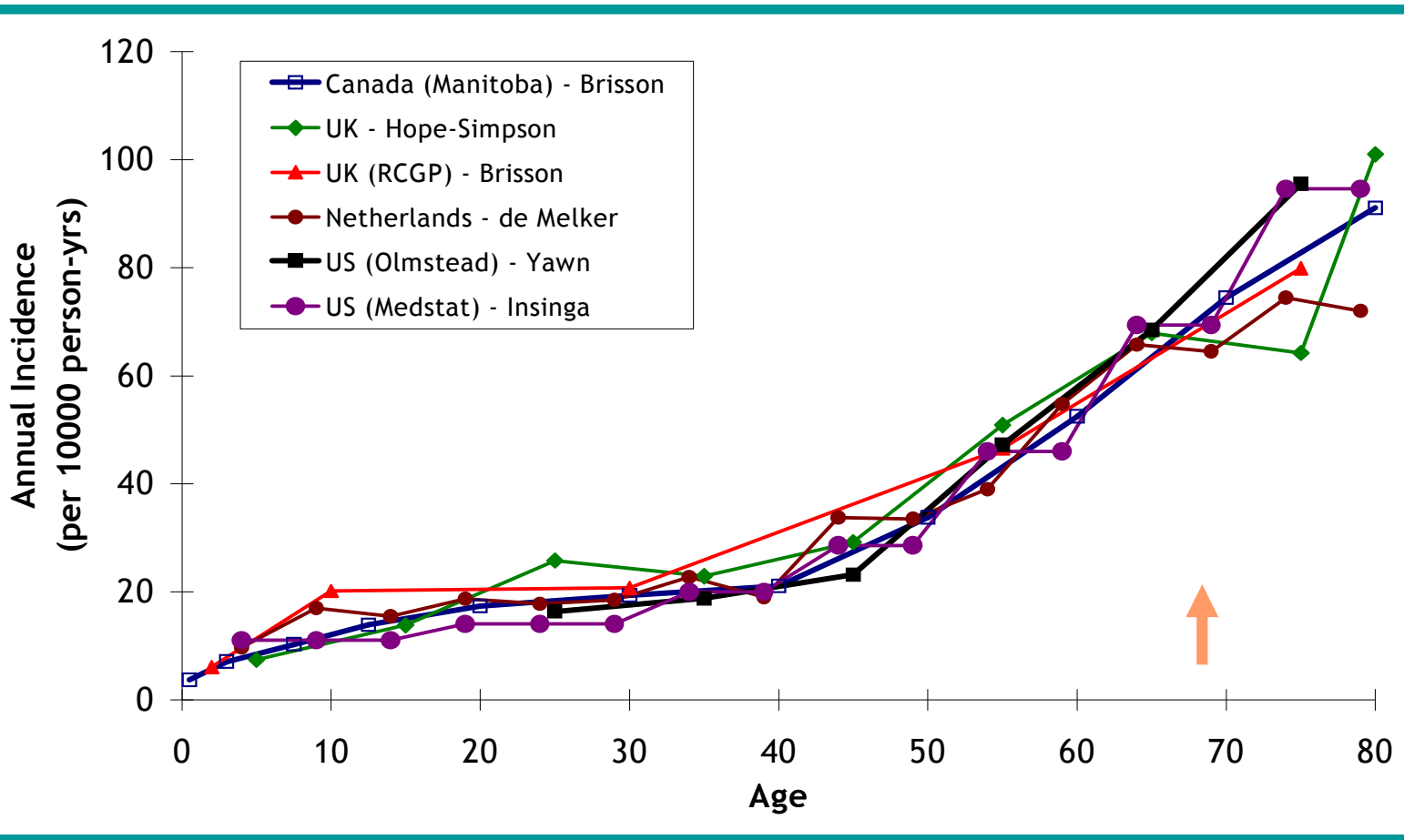
Seroconversion or 4x increase (%)



GMTR **ID** **IM**



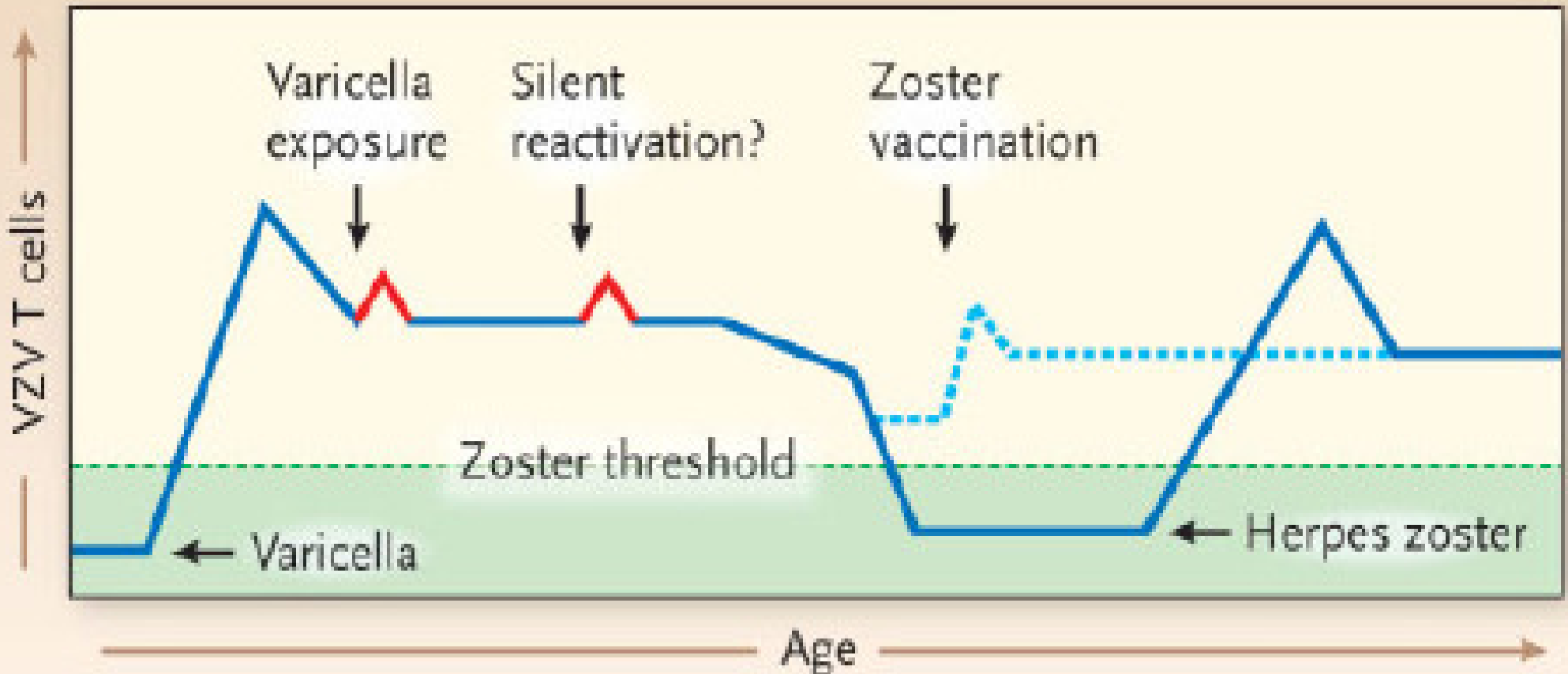
Herpes Zoster Incidence by Age



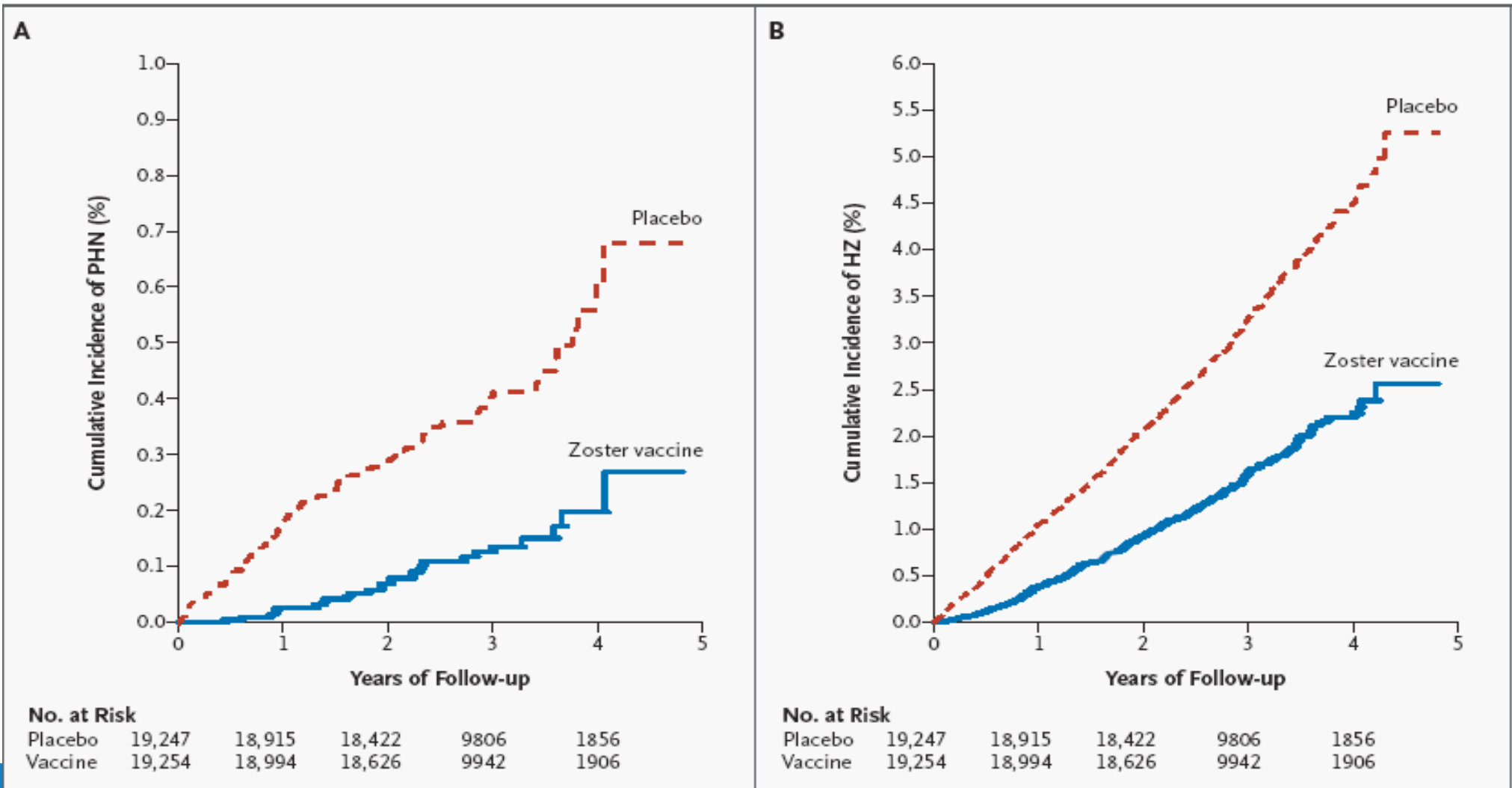
*Estimated 1 million cases per year in the United States**

*Insinga RP, Itzler RF, Pellissier JM, Saddier P, Nikas AA. *J Gen Intern Med.* 2005;20:748-753.

Host Factors in VZV Latency and Reactivation



Effect of Zostavax® on the Cumulative Incidence of PHN and HZ



Oxman MN, Levin MJ, Johnson GR, et al. *N Engl J Med*. 2005;352:2271–2284.



World Health Organization

Conclusions

- We are sitting on a time-bomb which has already begun to go off
 - In developing countries the elderly population is increasing rapidly and ill-health in this population is going to become a significant drain on limited resources
- Influenza and other vaccine-preventable infectious diseases contribute significantly to morbidity and mortality in the elderly
- The immune response in the elderly is diminished. This is possibly exacerbated by chronic viral infections (CMV, EBV) and renders standard vaccines less effective



Research is needed

- On immune function and causes of mortality of elderly in developing countries
 - Different environmental factors and exposure to disease
- Vaccines for the elderly aimed at overcoming immune sub-responsiveness



In all countries, and in developing countries in particular, measures to help older people remain healthy and active are a necessity, not a luxury.

