Hospitalisation: A Failure of Vaccination?

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Introduction to the talk

- "With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction…"

- Few would argue with Bill Gates who described vaccination as *"the most effective and cost-effective health tool ever invented"*.
- Vaccination has saved many lives and has the potential to save millions more, especially if vaccines are developed against the "big three"; malaria, HIV and TB.
- Vaccine development comes at a price that is not only financial but societal.

Plotkin S, Orenstein W, Offit P. *Vaccines*, 5th ed. Saunders, 2008
Sheehy S et al. Am Med Assoc J Ethics 2012; 14: 35-38

Introduction to the talk

- Immunization is a process whereby individuals are made immune to infectious diseases.
- This can be achieved through active immunity, whereby immunity is induced by vaccination with delivery of antigens to the individual.
- It can also be achieved by passive immunity, through the administration of antibodies to the individual.
- A small proportion of individuals remain prone to infection despite vaccination.
- Vaccine failures can be categorised as being primary or secondary.

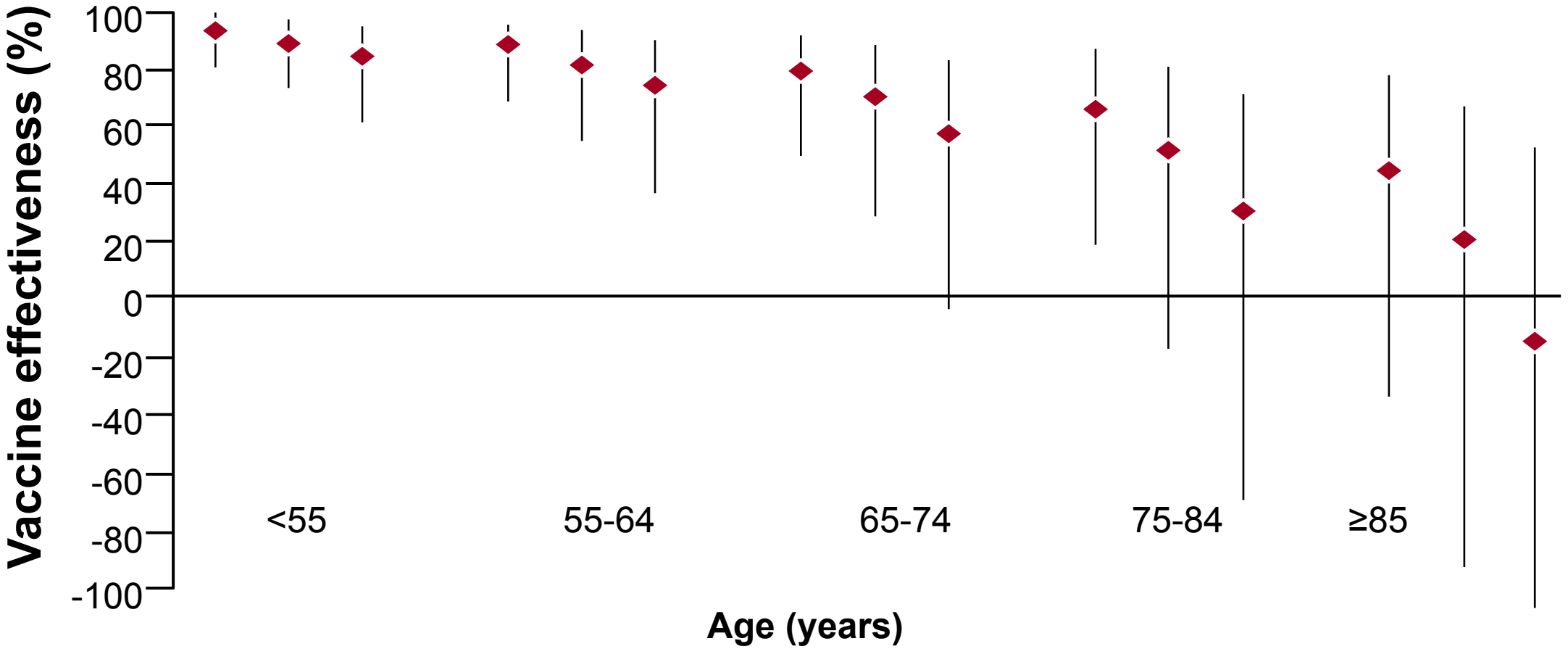
Galiza E et al. Medicine 2017; 45: 608-613

Definitions of vaccine failure

- Individuals with **primary vaccine failure** do not have any, or have an inadequate, immunological response to the vaccine.
- In those with **secondary vaccine failure**, there is an initial immunological response, but this wanes over time, leaving the patient susceptible again – booster doses may be needed.
- **Failure to vaccinate** is an additional concept, which indicates that failures occurred but vaccines were not given properly, including administration errors (wrong dose or route), incomplete series, or improper storage (e.g., cold chain failure) and others.
- It remains important to remember that despite their remarkable success globally, vaccines are neither 100% efficacious, nor 100% effective.

Galiza E et al. Medicine 2017; 45: 608-613
Heininger U et al. Vaccine 2012; 30: 1265-1268

PPV23 vaccine effectiveness against IPD



Jackson LA et al. Clin Infect Dis. 2008; 47: 1328-1338

Causes of vaccine failures

- **Host factors**
  - Genetics, immunosenescence, immunosuppression, underlying comorbidities e.g., obesity, cardiovascular disease, renal disease, poor nutritional status
- **Infection factors**
  - The circulating pathogen e.g., influenza strain drifts and shifts, or SARS-CoV-2 variants
- **Vaccine factors**
  - Missed opportunities to vaccinate, systematic risk factors such as intellectual disabilities, and administration errors

Galiza E et al. Medicine 2017; 45: 608-613
Heininger U et al. Vaccine 2012; 30: 1265-1268

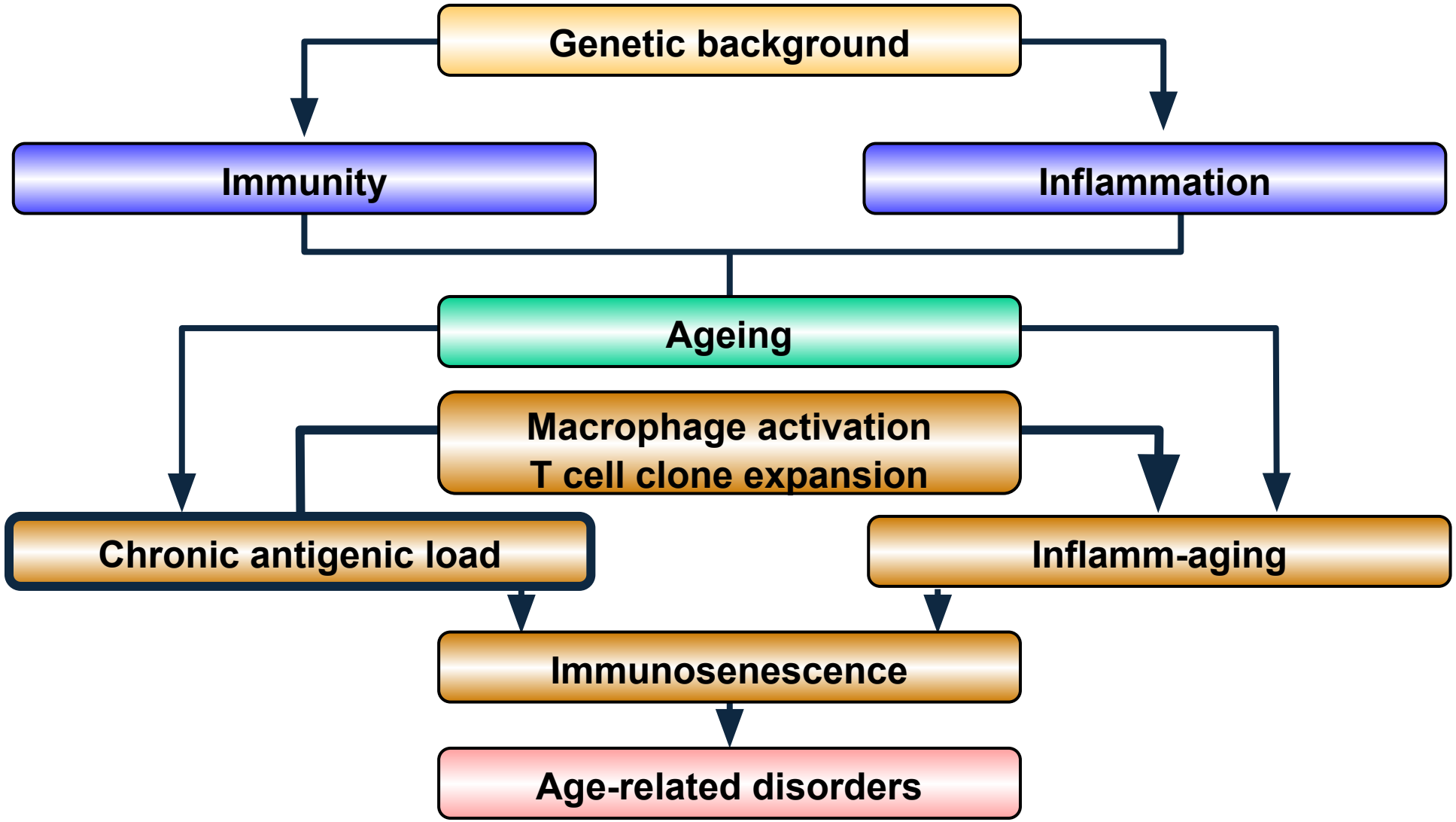
What is immunosenescence?

- The quality of the immune system declines with advancing age resulting in increased susceptibility to infection and pathological conditions relating to inflammation (co-morbidities) or autoimmune disease

- The change in the immune system that occurs with advancing age is termed immuno-senescence

Caruso C et al. Immun Ageing. 2009; 6: 10

Effect of genetic background and ageing on the immune system



Larbi A et al. Physiology. 2008; 23: 64-74

Challenges with vaccinating older individuals

- The elderly have reduced innate and adaptive immune function which results in:
  - Impaired local responses at the site of vaccine injection[1]
  - Reduced primary immune responses to new antigens[1]
  - Reduced efficiency for memory B cells and decrease revaccination response[1]
  - Reduced functionality of antibodies, and reduced phagocytic killing capacity of neutrophils[2]
  - Reduced long-term protective effect of vaccination[1]
- At the same time, vaccination is an important strategy to prevent infection and protect vulnerable, older people

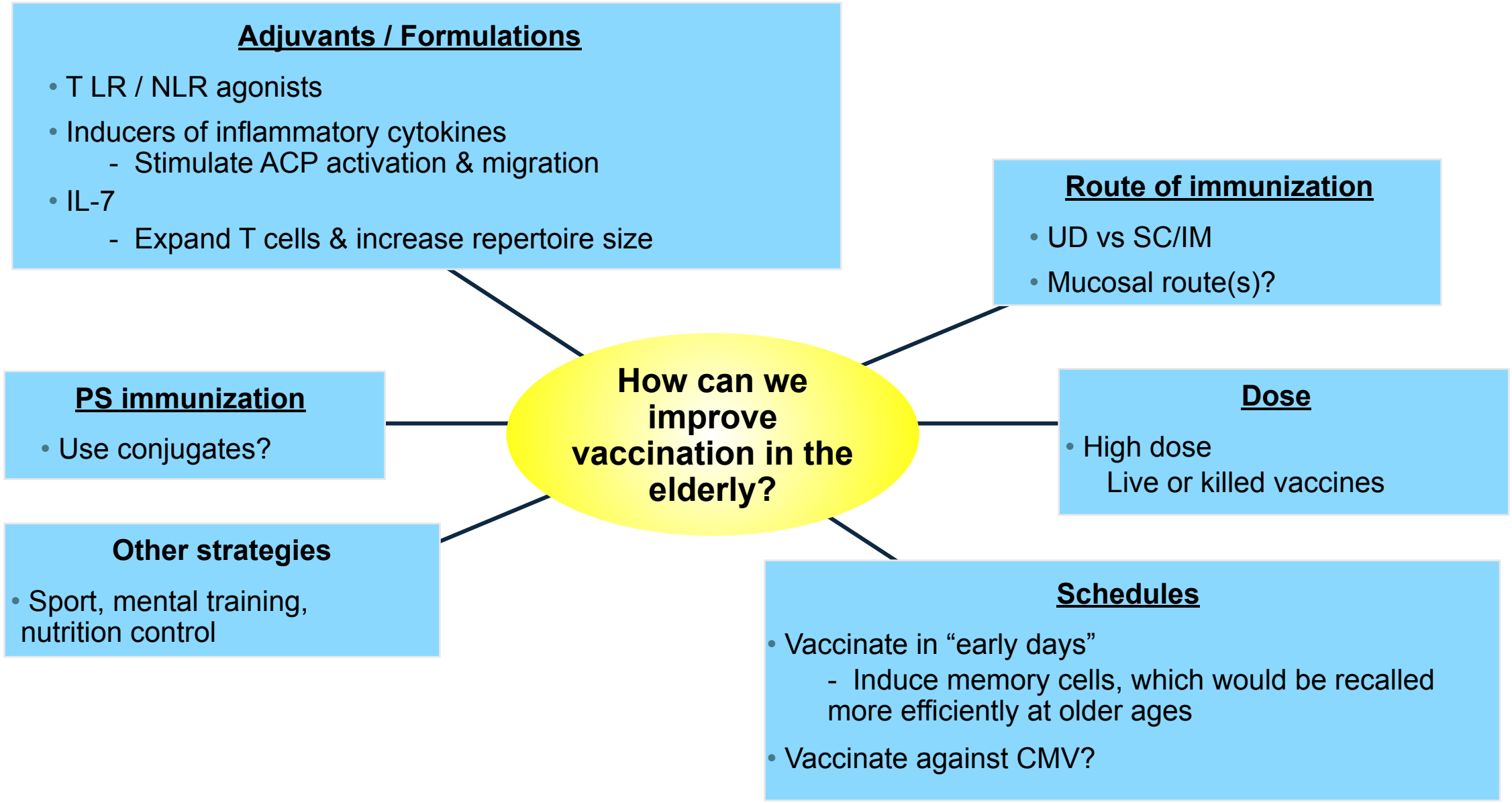
1. Weinberger B et al. Clin Infect Dis. 2008:46:1078-1084.
2. Simell B et al. Vaccine. 2011; 29(10): 1929-1934.

Attempts to restore immunity to the elderly

Intervention	Effects
Vitamin B6	+ Lymphocyte proliferation
Vitamin E	+ PPAR-α - Free radical production - Prostaglandin-E2
DHEA	- Prostaglandin-E2 - Inflammation
Vitamin D	- IFN-γ transcription - Th1/Th2 response
Zinc	+ vaccine reponses
Folate	+ Proliferative responses to mitogens + Distribution of T cells + Cytokine production in the spleen
PUFA	- T-cell activation - T-cell signalling - Lymphocyte proliferation
Probiotic	+ Number of CD4+ and CD25+ T cells
(Biofidobacterium lactis HNO19)	+ Number and activity of natural killer cells + Phagocytic capacity

Larbi A et al. Physiology. 2008; 23: 64-74

Strategies to improve vaccine efficacy in the elderly



Guy B. J Comp Path 2010; 142: S133-S137

True failures of vaccination

- About 2–10% of healthy individuals fail to mount antibody levels to routine vaccines.
- Comparing the IR to different vaccines in non-responder and high-responder vaccinees revealed hypo-responsiveness is antigen/vaccine-specific at the humoral, but not the cellular level.
- T-regulatory as well as B-regulatory cells and the production of IL-10 are involved in non/hypo-responsiveness.
- Non-responsiveness increases with age and occurs in particular with a novel vaccine in persons >65 years, indicating that vaccine schedules and doses (at least for primary vaccination) should be adapted according to age.

Wiedermann U et al. Human Vaccines & Immunotherapeutics 2016; 12; 239--243

Apparent failures of COVID-19 vaccination

- The ISARIC4C protocol, analysed UK hospital admissions after the start of the COVID-19 vaccination rollout.
- As of 10 April 2021, 3842 of the 99 445 inpatients enrolled in the study had been vaccinated.
- Looking at symptomatic patients (1823), the researchers found that 40% (729) developed COVID-19 symptoms 0-7 days post-vaccination.
- A further 19% (352) developed symptoms 8-14 days post-vaccination.
- The median incubation period for SARS-CoV-2 is around five days, meaning it is likely that many of these patients were infected before immunity developed.

Mahase E. BMJ 2021; 373: n1127

Impact of vaccination on hospital course

- While vaccination may not always prevent hospitalisation it does alter the hospitalisation experience in those who do get sick
  - Significant reduction in severe complications such as pneumonia, bacterial superinfection, acute respiratory distress disorder, and multiorgan failure
  - Reduced need for ICU admission or mechanical ventilation
  - Shorter hospital stay compared to those not vaccinated
  - Lower overall economic costs for all the above reasons
  - In some studies there is reduction overall in mortality

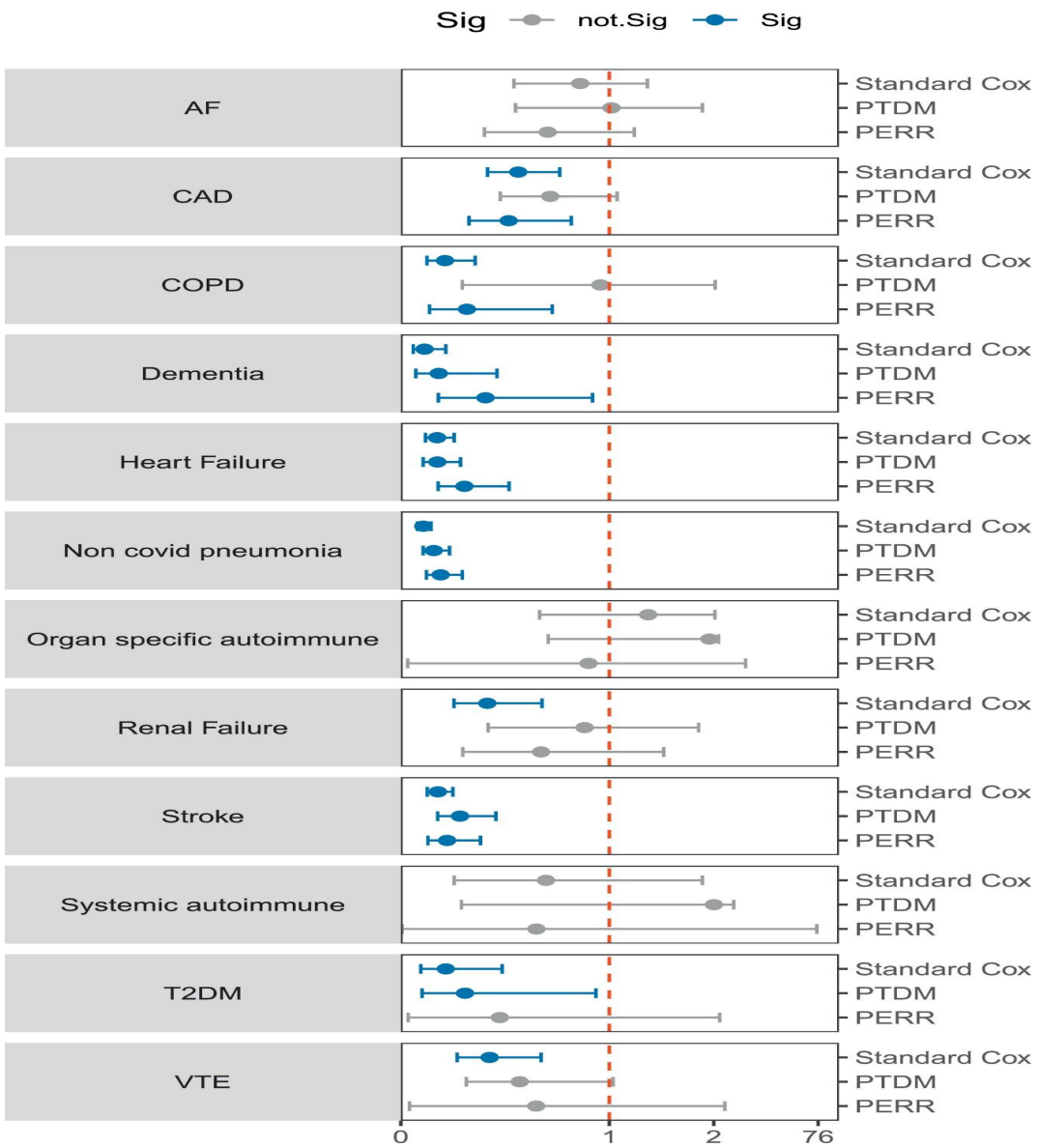
Mongas-Moto A et al. Am J Infect Control 2024; 52(5): 563-5699

Additional benefits of COVID-19 vaccination

- Because COVID-19 may be associated with various complications, such as cardiovascular events, renal failure, and other diseases, it is reasonable to hypothesize that COVID-19 vaccination may reduce risks of these complications.
- Influenza vaccination has been associated with reduced cardiovascular risks and mortality, primarily due to a decrease in flu infection; however, flu vaccines may also promote plaque stabilization and nitric oxide production.
- It is plausible that COVID-19 vaccination may also reduce cardiovascular risks and other relevant sequelae.
- This study investigated the association of COVID-19 vaccination with hospitalization from cardiovascular and exacerbations of other comorbid conditions in the short term.

Xiang Y et al. International Journal of Infectious Diseases 2024; 145: 107080

Additional benefits of COVID-19 vaccination



Xiang Y et al. International Journal of Infectious Diseases 2024; 145: 107080

Hospitalisation: A failure of vaccination?

- No vaccine has 100% efficacy and/or 100% effectiveness.
- True vaccine failure is uncommon but does sometimes occur.
- Age and underlying comorbidity (obesity) may play a role.
- Failure to vaccinate (correctly) is a much greater issue.
- It is important to evaluate the benefits of vaccination appropriately.
- Hospitalisation for infection following vaccination may be associated with an improved hospital experience.
- Hospitalisation for cardiovascular events and exacerbations of comorbid conditions may be reduced by vaccination.
- Vaccines do reduce mortality.

Thank you!