Non-specific immunological effects of vaccines

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**Immune system**

**Innate immunity**
- Fast (minutes)
- Broad range
- No memory

- Phagocytosis
- Microbial killing
- Cytokines:
  - IL-1β
  - TNF-α
  - IL-6

**Adaptive immunity**
- Slower (days)
- Specific
- Immunological memory

- Antibodies
- Cytokines:
  - IFN-γ
  - IL-17
  - IL-22

Adapted from Dranoff, Nat Rev Cancer 2004
Classical principle of vaccination

- Vaccine is recognized by adaptive immune system
- Adaptive immunological memory is built
- Stronger antibody response upon infection leads to protection

Siegrist CA. Vaccine Immunology 2008
Trained immunity

- Memory of innate immune system
- Mediated by epigenetic changes
- Training stimulus leads to altered immune response upon infection
- Cytokines
  - TNF-α, IL-1β, IL-6
Infection or vaccination

Epigenetic reprogramming in innate immune cells

Trained immunity transcriptional & functional programs

Adaptive states
- Mucosal tolerance
- Limitation of tissue damage in infection

Maladaptive states
- Immune paralysis in sepsis

Tolerance programs
- Innate immunity maturation
- Nonspecific protection by vaccines

Training programs
- Hyperinflammation in tissues
- Atherosclerosis

Adapted from: Netea et al. Science 2016
**Heterologous adaptive immunity**

- Adaptive immune cells respond to unrelated pathogens
  - Cross-reactivity
  - ‘Bystander activation’

- Cytokines
  - IFN-γ, IL-17, IL-22

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Non-specific effect of BCG

- BCG vaccination leads to increased cytokine responses to unrelated antigens
- Associated with increased active epigenetic marks
- Also shown in neonates

Kleinnijenhuis et al. PNAS 2012
Vitamin A modulates trained immunity

- Vitamin A inhibits cytokine production
- Vitamin A inhibits BCG-induced trained immunity
- Different interventions can interact

Arts et al. JLB, 2015
Arts & Benn, Sight and Life, 2015
Not all vaccines are equal

- Live Vaccinia induces trained immunity
- Non-replicating Vaccinia induces immune tolerance

Blok et al, unpublished data
Negative heterologous effects - DTP

In children DTP reduces innate immune response to unrelated stimuli – different for boys and girls

Noho-Konteh et al. CID 2016
Concluding

• Vaccines confer specific protection against disease through adaptive immune memory

• Vaccines also modulate the immune response to unrelated pathogens, i.e. have non-specific effects
  – Trained immunity
  – Heterologous adaptive immunity

• This can lead to enhanced or reduced immune responses depending on vaccine
  – Enhanced by live vaccines: BCG, Vaccinia
  – Decreased by inactivated vaccines: MVA, Salmonella, DTP