Australian Vaccinology Course 2026

Non-Targeted Immunomodulatory Effects of Vaccines

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Accepted Vaccine Paradigms

Vaccines have targeted effects against the vaccine targeted disease only

Males and females respond equally to vaccines

They can be given in any order and combination

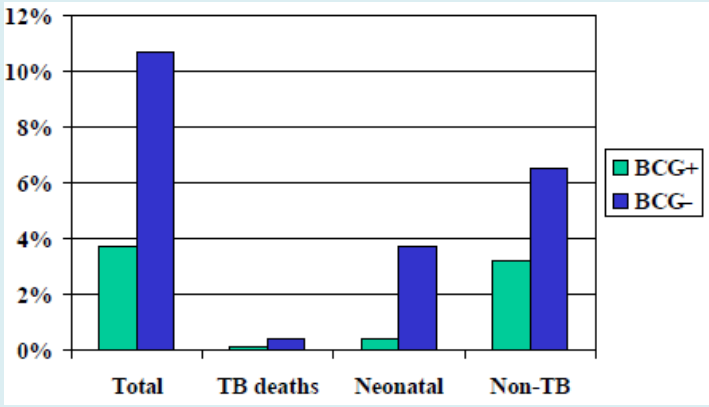
A New Paradigm in Vaccinology

- **Non-Specific Effects (NSE) - the original epidemiological term**
- Also called: heterologous effects, off-target effects, non-targeted effects, disease agnostic effects, immunomodulatory effects
- In plain terms: a vaccine can shift your risk of illness and death from diseases it was never designed to prevent — for better or for worse

The First Clue: Sweden, 1927–32

BCG was introduced to prevent tuberculosis.
Naeslund noticed something unexpected: vaccinated children had markedly fewer deaths from causes that had nothing to do with TB.

"One could obviously be tempted to find an explanation for this lower mortality of vaccinated children in the idea that BCG vaccine provokes a non-specific immunity…"



Carl Naeslund, 1932, on BCG mortality data from Norrbotten, Sweden

HISTORY

The High-Titre Measles Story

1989

WHO recommends high-titre measles vaccine (HTMV) at 6 months in high-mortality settings

1987–92

Trials in Senegal, Guinea-Bissau, Haiti: HTMV protects against measles infection…

1991

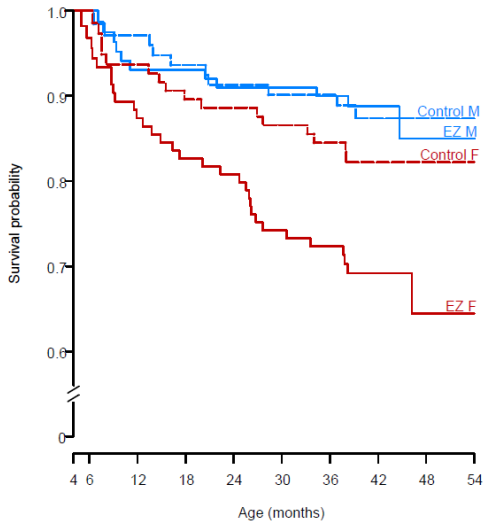
…but girls given HTMV show higher all-cause mortality than boys, or than girls given standard vaccine

1992

WHO withdraws its HTMV recommendation

2003

Later analysis shows the excess mortality tracked a subsequent DTP dose, not HTMV itself



EZ = HTMV at 4m, IPV at 9m
Control = IPV at 4m, MV at 9m

First widely accepted evidence of altered all-cause mortality after vaccination and sex differences in this effect

Aaby et al. Lancet 2003;361:2183

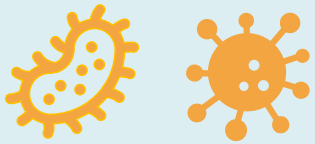
Live Vaccines Beneficial. Killed Vaccines May Have Negative Immunomodulatory Effects.

30–50%

Reduction in all-cause mortality associated with BCG vaccination particularly neonatal mortality

30–86%

Reduction in all-cause mortality associated with measles vaccination, beyond measles prevention alone

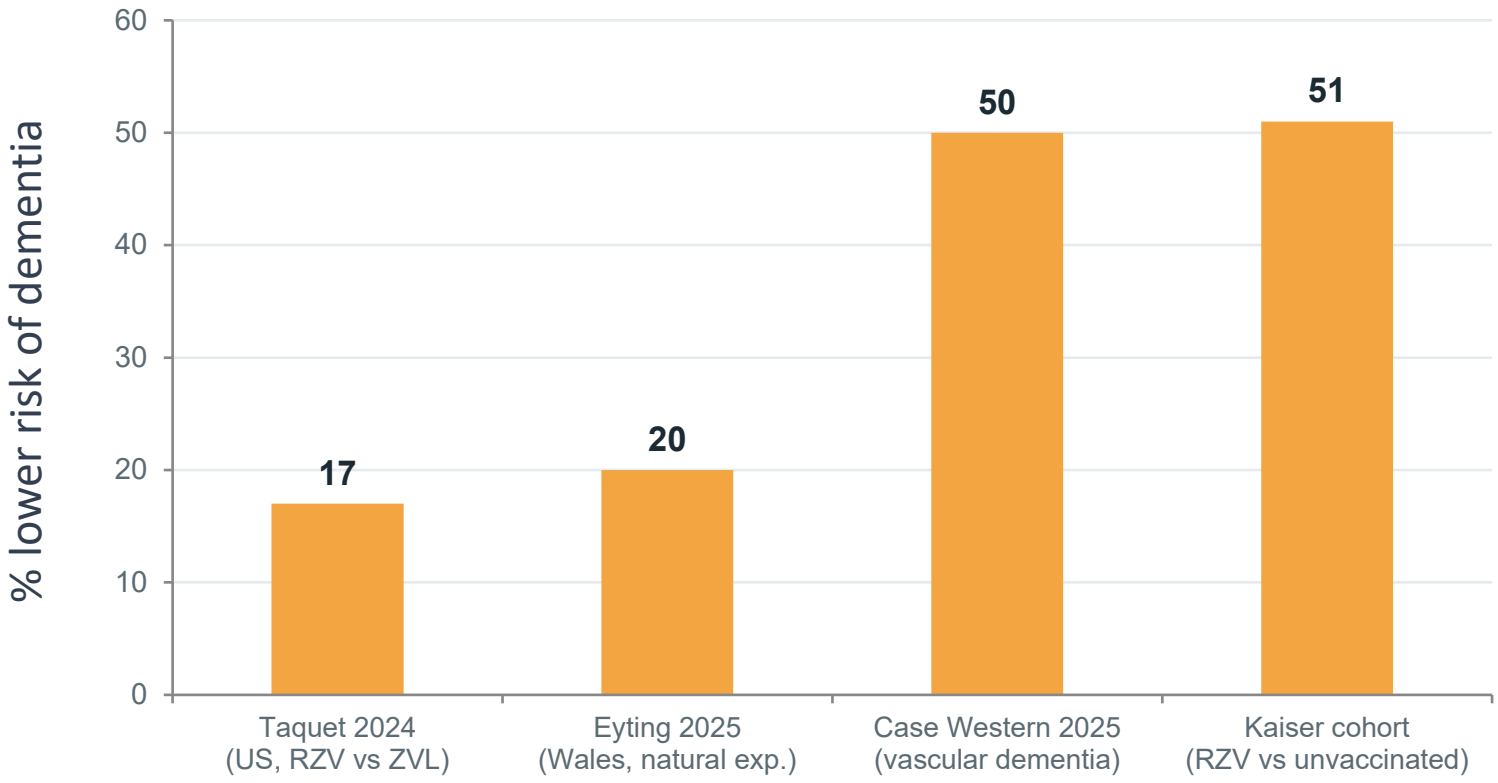


Signal of increased mortality and infections associated with whole-cell DTP (DTwP), a killed vaccine

- Effects are strongest in the first 6 months after vaccination.
- Combining a live vaccine with a killed one can blunt the live vaccine's benefit.
- Effects are consistently sex-differential, generally being stronger in females than males for both beneficial (measles, BCG) and deleterious (DTwP) outcomes.

Flanagan KL et al. Clin Infect Dis 2013;57:283; Klein SL, Flanagan KL. Nat Rev Immunol 2016;16:626; Aaby P et al. Lancet 2003;361:2183

A New Signal: Zoster Vaccine and Dementia Risk



- Findings replicated across several independent natural experiments and cohorts — addressing earlier confounding concerns
- Benefit seen in both sexes, but generally larger in women
- Effect sizes vary by design and comparator vaccine, but direction is highly consistent

Taquet M et al. Nat Med 2024;30; Eyting M et al. Nature 2025; IDWeek 2025 (Case Western, preprint); Kaiser Permanente cohort, Nat Commun 2025

POTENTIAL MECHANISMS

What are the Mechanisms?

Trained Immunity: A New Kind of Immune Memory

- Textbook immunology held that only T and B cells have ‘memory’ — innate cells like monocytes were thought to behave predictably and identically every time they are activated i.e. don’t have memory

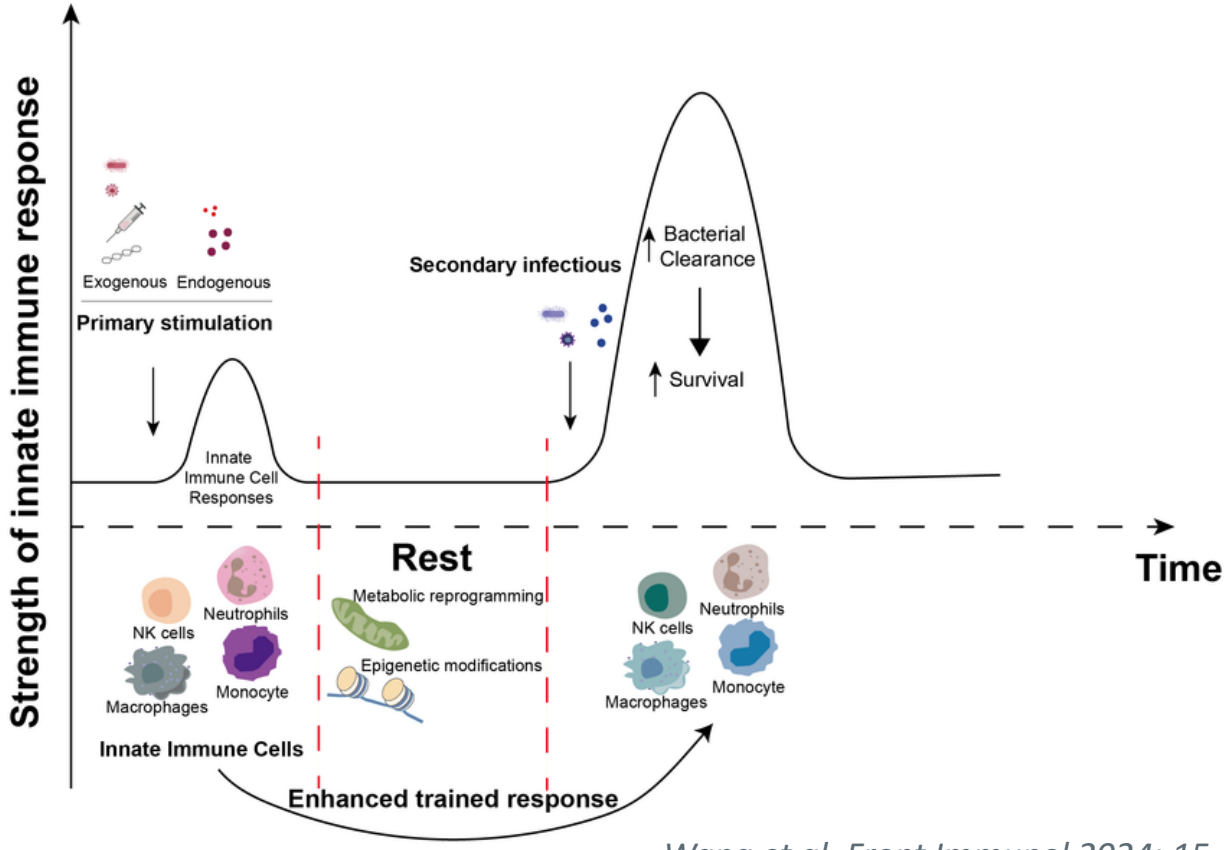
2011–12: the breakthrough

- Netea and colleagues showed monocytes exposed to BCG mount a stronger response to a second, unrelated stimulus weeks later, including unrelated pathogens such as *C. albicans*, *S. aureus*
- This functional reprogramming of innate immune cells was termed ‘trained immunity’
- For the first time, this offered a plausible cellular mechanism for the epidemiological beneficial signal first noted for BCG in the 1930s

Netea MG et al. Science 2016;352:aaf1098; Kleinnijenhuis J et al. PNAS 2012;109:17537

How BCG 'Trains' Innate Cells

- BCG is sensed via the innate pattern-recognition receptor on innate cells
- This triggers durable epigenetic marks — histone modifications at the promoters of inflammatory genes — without changing the DNA sequence
- Cells undergo metabolic reprogramming e.g shift toward glycolysis, priming cells for a faster, larger response on re-challenge
- Net result: monocytes and macrophages respond more vigorously to a second, unrelated pathogen, e.g. *Staphylococcus aureus*, *Candida albicans*



Wang et al. Front Immunol 2024; 15

Sex-Differential Non-Vaccine-Specific Immunological Effects of Diphtheria-Tetanus-Pertussis and Measles Vaccination

Noho-Konteh F, Adetifa JU, Cox M, Hossin S, Reynolds J, Le MT, Sanyang LC, Drammeh A, Plebanski M, Forster T, Dickinson P, Ghazal P, Whittle H, Rowland-Jones SL, Sutherland JS, Flanagan KL

Clin Infect Dis 2016; 63(9): 1213–1226

- Prospective immunological study of 302 Gambian infants receiving DTP and/or measles vaccine (MV) or both together
- Differential gene expression analysed at 24 hours by RNAseq
- Cytokine responses measured by 27-plex bead array in plasma and stimulated whole blood
- Immune cell subsets analysed by multi-colour flow cytometry

Key findings

DTP had an immunosuppressive effect on innate pro-inflammatory gene expression and T-cell immunity, specifically in females

Measles vaccine enhanced pro-inflammatory innate responses in males only, not females

n=302

Gambian infants studied

♀ DTP ↓

↓ Innate & T-cell responses in girls

♂ MV ↑

↑ Innate pro-inflammatory boost in boys

IMPLICATIONS

Relevance to Future Vaccine Policy

IMPLICATIONS

Why Does This Matter?

Dosing

Sex-adjusted vaccine dosing could reduce adverse events without sacrificing protection — e.g. half-dose influenza vaccine in women

Scheduling

The order in which vaccines are given may need to be actively managed, not left to convenience

Risk of Withdrawing Beneficial Vaccines

Removing a vaccine with beneficial immunomodulatory effects (e.g. BCG, OPV) after disease eradication could paradoxically increase mortality

Pharmacovigilance

Unexpected sex-differential signals have appeared for newer vaccines, e.g. young male myocarditis with mRNA COVID vaccines; older female TTS risk with AZ COVID vaccine; excess female mortality after the RTS,S malaria vaccine.

Supports monitoring for all-cause, not just disease-specific, outcomes

WHO SAGE Systematic Review, 2014

- **Terms of reference:**
  - Review the evidence for non-specific effects of vaccines in the routine infant schedule, and determine whether it justifies a policy change
- **Conclusions:**
  - Epidemiological evidence supports protective heterologous effects of BCG and measles vaccine
  - Evidence for deleterious effects of whole-cell DTP (DTwP) was judged insufficient
  - Not enough evidence, at the time, to justify changing vaccine policy or scheduling
  - Called for more studies — specifically powered by sex, and including detailed immunological mechanism work

- The Optimmunize Consortium convened Wellcome Trust funded international meetings in UK in 2020 and 2026.
- 2020 meeting opened by WHO Director General Tedros Ghebreyesus who acknowledged that the non-targeted effects of vaccines need to be considered in vaccine policy.
- Both meetings had session at the end with WHO representation to discuss policy implications.

WHO. Wkly Epidemiol Rec 2014;89(21):221–236

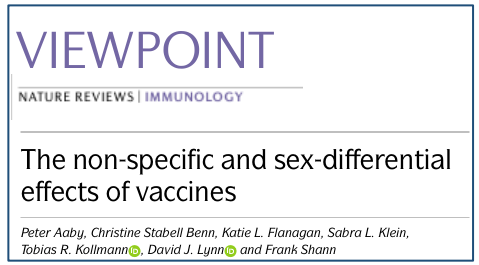
Research Priorities & Knowledge Gaps

- Mechanistic, prospective human studies — not just epidemiology — spanning the life course
- Routine sex-disaggregation of vaccine trial data as standard practice, not an afterthought
- Randomised trials to confirm causality
- Translating immunological mechanisms into next-generation adjuvants / vaccines deliberately designed for heterologous benefit
- Harmonised international surveillance for unexpected all-cause morbidity/mortality signals after new vaccine introductions


frontiers in Immunology

Grand challenges in sex differences in immunology: problems the field must solve before biological sex can guide clinical practice

Katie L. Flanagan and Susan Kovats


VIEWPOINT

NATURE REVIEWS | IMMUNOLOGY

The non-specific and sex-differential effects of vaccines

Peter Aaby, Christine Stabell Benn, Katie L. Flanagan, Sabra L. Klein, Tobias R. Kollmann, David J. Lynn and Frank Shann


Drug Safety (2023) 46:439–448
https://doi.org/10.1007/s40264-023-01295-3

CURRENT OPINION

Implications of Non-Specific Effects for Testing, Approving, and Regulating Vaccines

Christine Stabell Benn · Nelly Amenyogbe · Anders Björkman · Jorge Domínguez-Andrés · Eleanor N. Fish · Katie L. Flanagan · Sabra L. Klein · Tobias R. Kollmann · Kirsten Ohm Kyvik · Mihai G. Netea · Naja Hulvej Rod · Frederik Schaltz-Buchholzer · Frank Shann · Liisa Selin · Sanne M. Thysen · Peter Aaby


PLOS Biology

ESSAY

Knowledge gaps and research priorities to understand sex differences in immunity

Katie L. Flanagan, Sabra L. Klein

Thank You & Questions ?