What we learned from studying the overall health effects of vaccines: Non-specific effects and sex-differences

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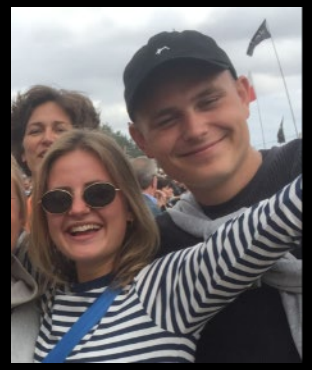
Disclaimer

- MD, PhD, DMSc, Epidemiologist
- Mother of two kids, who received all the vaccines in the Danish programme
- Spent part of the last 28 years in Africa, studying the overall health effects of vaccines
- Co-developer of the concept of *non-specific effects of vaccines*
- No other conflicts of interests



Primary sources of funding: ERC, Danish National Research Foundation, EU, EDCTP, Danish Medical Research Council, Danida, and many more

The current paradigm for vaccines

- A **vaccine** is a biological preparation that improves immunity to a particular disease

- **Evaluation and monitoring** is based on (biomarkers for) the **vaccine disease** and **assessment of potential plausible side effects**
  - Phase 3 trials
  - Post-marketing surveillance / (Phase 4 trials)

- None of the currently used vaccines were tested for their effect on the immune system and its ability to handle *other infections*

  Assumption: the immune system does not learn anything from meeting one pathogen that is used in the meeting with other pathogens

- The **effect on overall health** – "Will I be healthier from taking this vaccine?" – is based on extrapolations from the effect on the vaccine disease

Protective effect
against vaccine disease

=

Effect on
overall health

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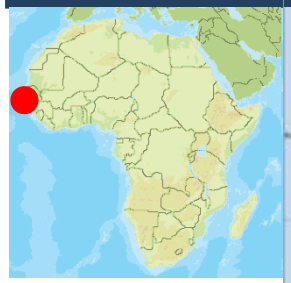
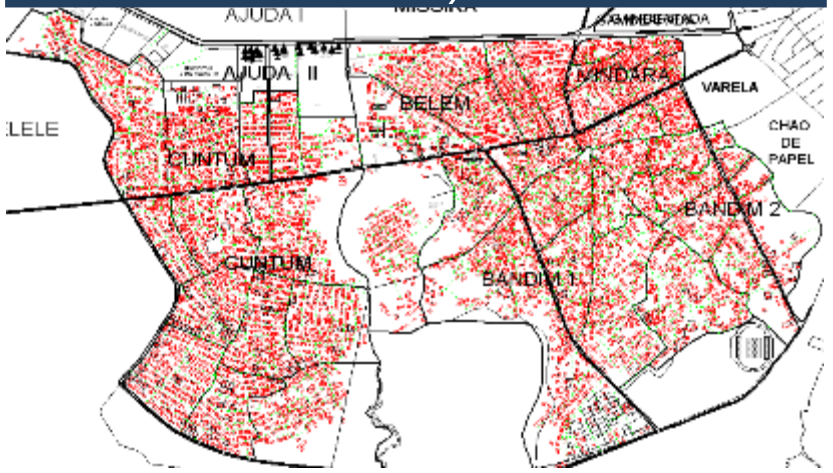
Guinea-Bissau



Bissau City

Urban study area



Rural study area

Urban study area: **> 100,000 persons**
Rural study area **: > 100,000 persons in 222 villages**

An African field station

Belem

Main road

Zona 6

Zona 5

170

Zona 8

Bandim 1

Zona 2

Zona 1

Zona 7

23

36

15

Zona 9

Regular home visits

Vital status, infections, vaccinations

Health centres and hospital

Vaccinations and hospitalisations

Vaccinations

Overall mortality and morbidity

Evaluation of vaccine effects

Protective effect
against vaccine disease

=

Effect on overall health

Evaluation of vaccine effects

Protective effect
against vaccine disease

+

Non-specific effect
on other diseases

=

Effect on overall health

Live vaccines

Examples:

Measles/Measles-mumps-rubella
Oral polio vaccine
Tuberculosis (BCG or ”Calmette”)
Smallpox
Intranasal influenza vaccine

Non-live vaccines

Examples:

Diphtheria-tetanus-pertussis (DTP)
Inactivated polio vaccine
Pneumococcal vaccine
HPV
Hepatitis B vaccine
Injectable Influenza vaccine

Our main research finding:
Non-specific effects of vaccines

Vaccines protect against the target disease, but have also important **non-specific effects (NSEs)** – affecting the susceptibility to other infectious diseases than the vaccine disease

- **Live vaccines** *(measles vaccine, BCG, smallpox vaccine, OPV)* have **beneficial NSEs**, protect against unrelated infections, and reduce all-cause morbidity and mortality

- **Non-live vaccines** *(DTP vaccine, Hep B vaccine, Pentavalent vaccine, Influenza vaccine, Inactivated polio vaccine, RTS,S)* have **harmful NSEs**, increase risk of unrelated infections, and increase all-cause morbidity and mortality in females - in spite of specific disease protection

Two propositions

- Vaccines do not only have specific effects
  - Ex. BCG vaccine against tuberculosis

- We can do harm if we focus on the specific effects of vaccines
  - Ex. DTP-vaccine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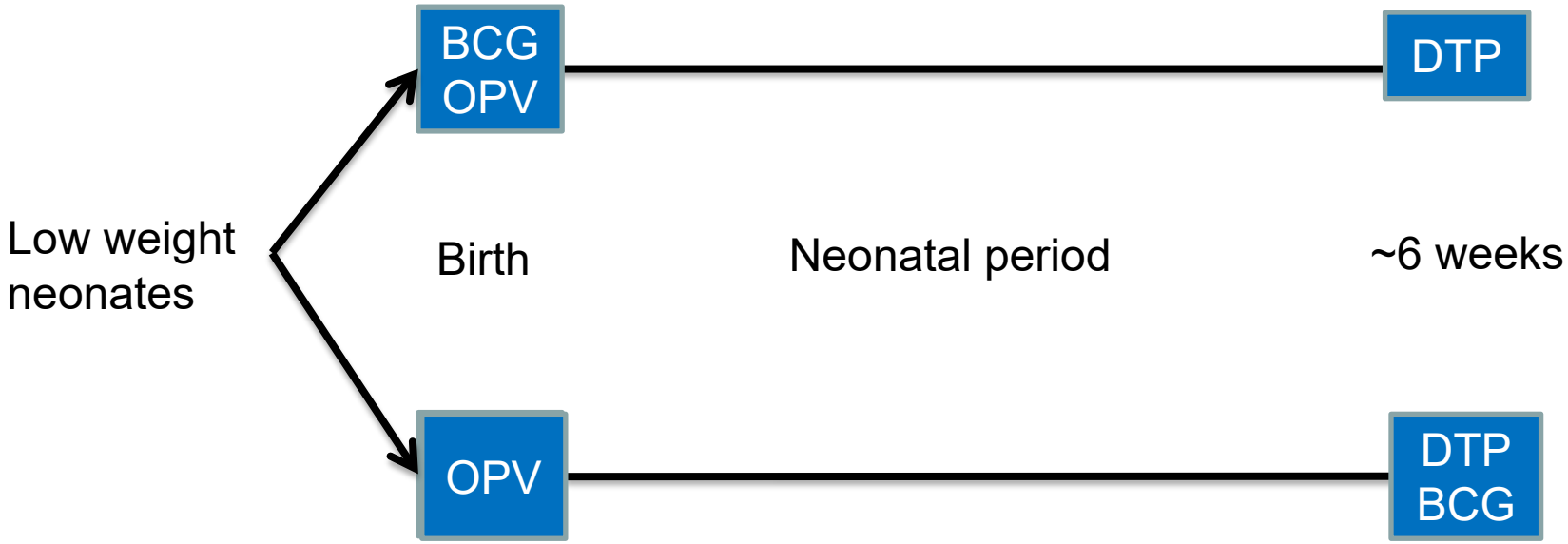
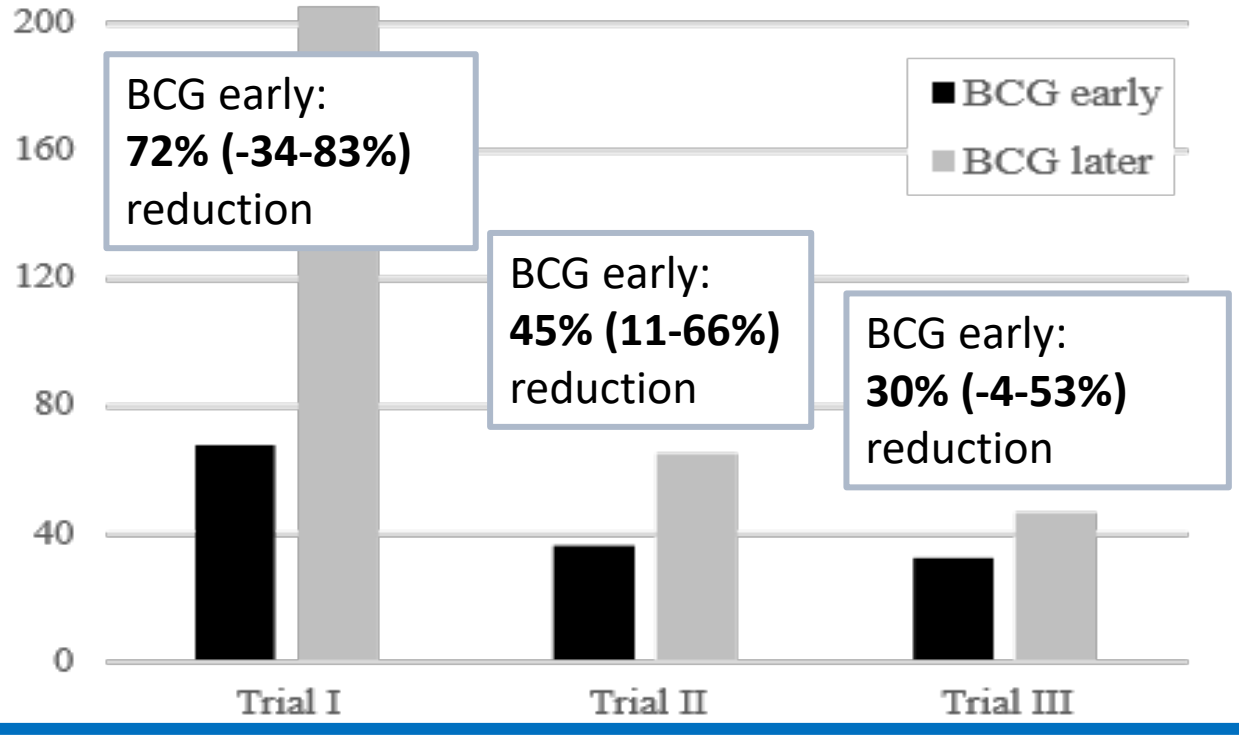
Testing non-specific effect of BCG vaccine in Guinea-Bissau
Randomised trial: BCG at birth or the usual delayed BCG



Biering-Sørensen et al, Clin Inf Dis 2017

Randomised trials: BCG at birth or the usual delayed BCG: Effect on neonatal mortality



Combined analysis **38% (17-54%) reduction in all-cause neonatal mortality**

Mainly due to ***non-specific protection*** against septicaemia and respiratory infections

Biering-Sørensen et al, Clin Inf Dis 2017. Just confirmed by Prentice et al, Lancet Infect Dis 2021

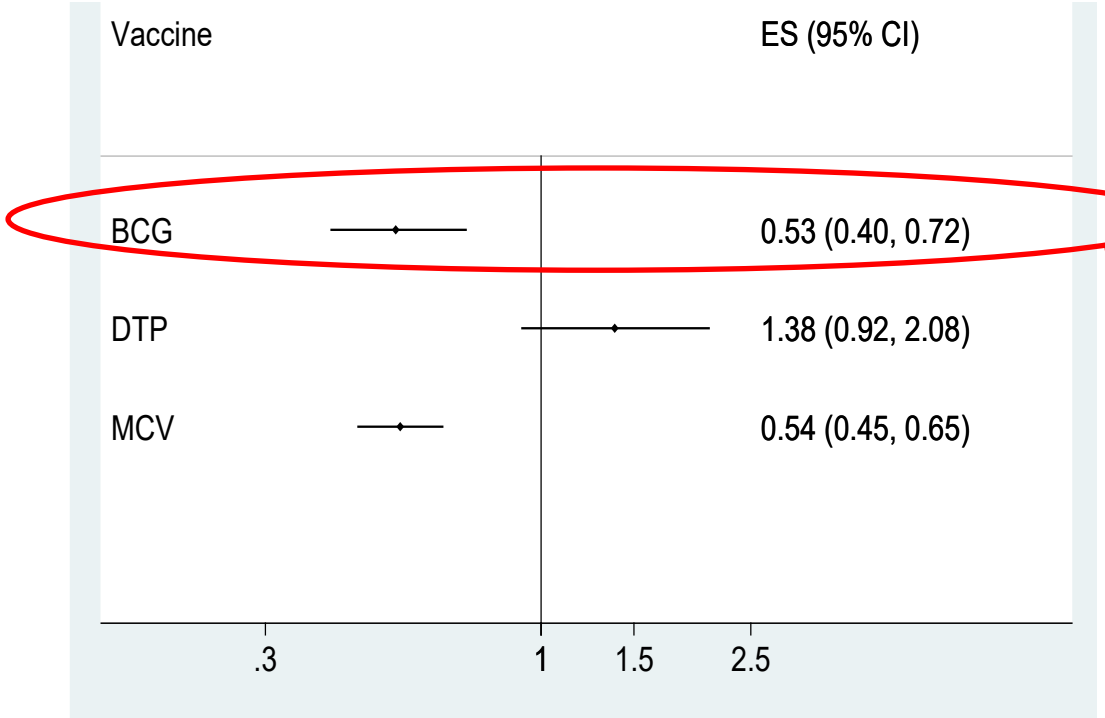
WHO review of non-specific effects, 2014

Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review

Julian P T Higgins,[1] Karla Soares-Weiser,[2] José A López-López,[1] Artemisia Kakourou,[3] Katherine Chaplin,[1] Hannah Christensen,[1] Natasha K Martin,[1,4] Jonathan A C Sterne,[1] Arthur L Reingold[5]

the bmj | *BMJ* 2016;355:i5170 | doi: 10.1136/bmj.i5170

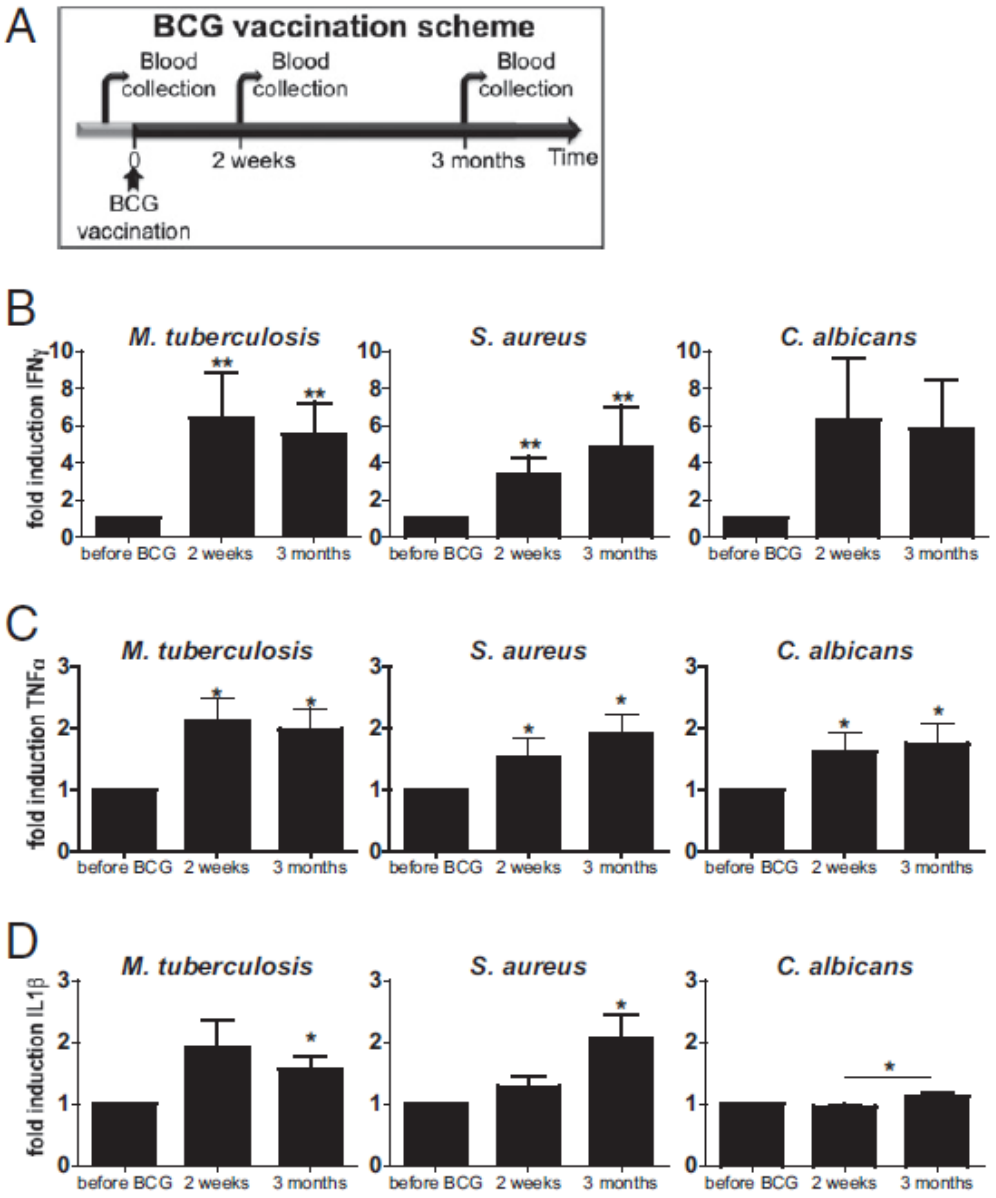
Receipt of BCG and measles containing vaccines may reduce overall mortality by more than expected through their effects on the diseases they prevent, and receipt of DTP may be associated with higher all cause mortality



Metaanalysis of 5 randomised trials and 9 observational studies

Higgins et al, BMJ 2016

Immunological mechanisms: ”Innate immune training”



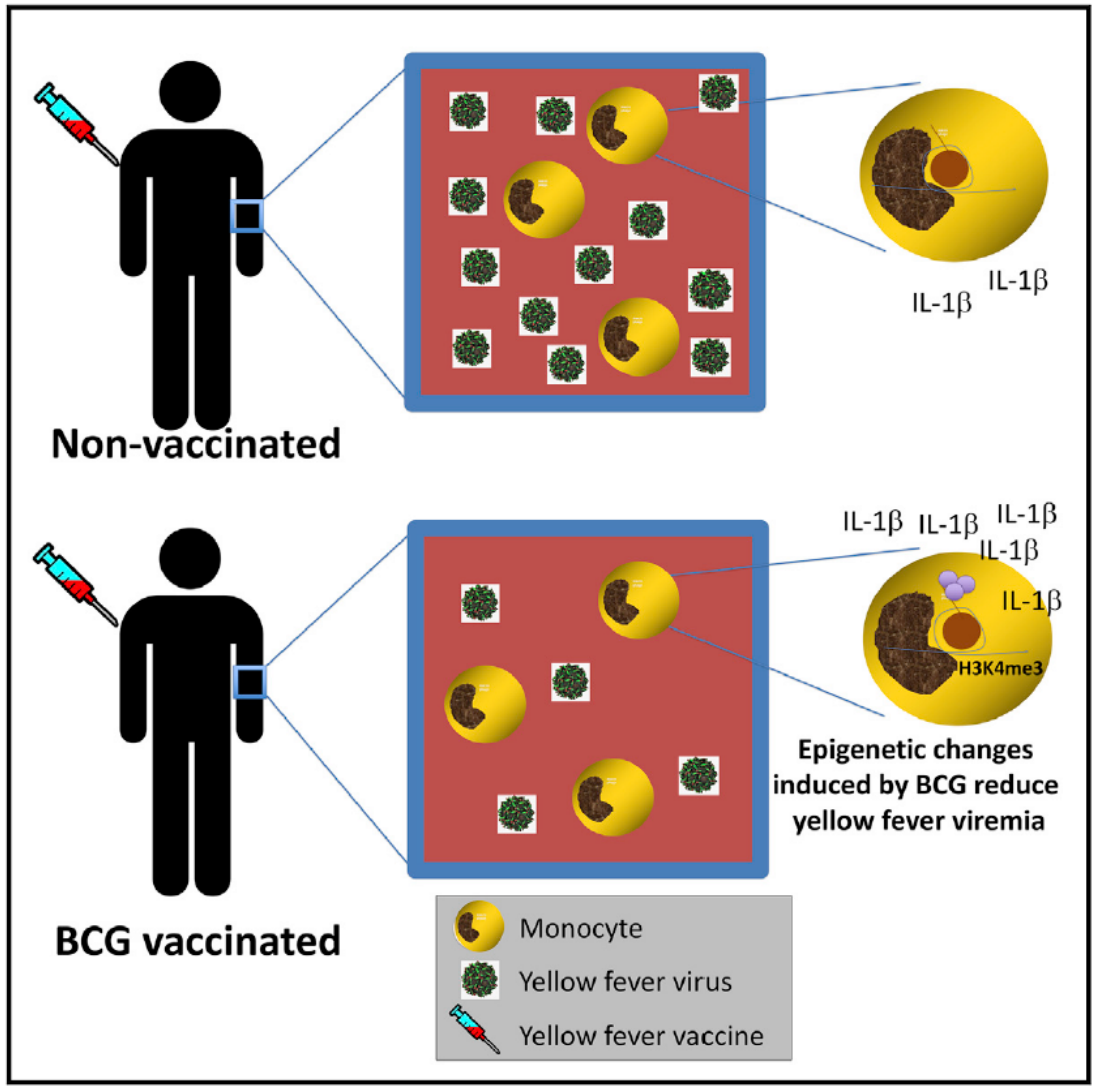
”Innate immune training”:

BCG associated with increased *in vitro* pro-inflammatory cytokine responses to non-specific stimulants after 2 weeks and 3 months

Mediated via epigenetic modifications of the innate immune cells

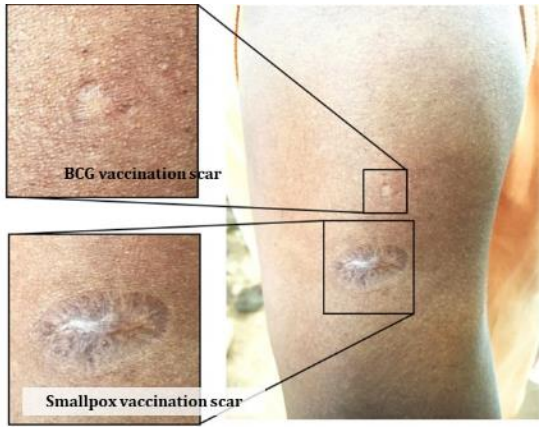
Kleinnijenhuis et al, PNAS 2012

Immunological mechanisms: ”Innate immune training”
Proof of principle:
BCG 4 weeks prior to yellow fever vaccine reduces viremia in a human infectious challenge model



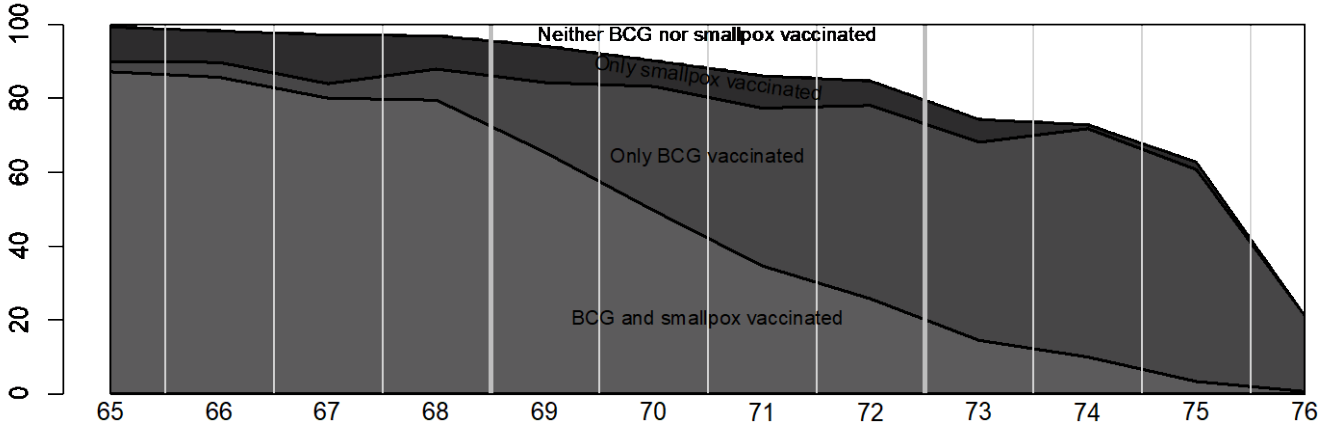
Arts et al, Cell Host Microb 2018

BCG, smallpox and mortality among adults in Denmark



Both vaccines leave characteristic scars

BCG and smallpox phased out in birth cohorts 1965-1976



BCG and/or smallpox vaccination vs neither:
46% (19%-64%) lower mortality from natural causes up to 45 years of age

Rieckmann et al, Int J Epidemiol 2017

Non-specific effects of live vaccines against COVID-19?

Can existing live vaccines prevent COVID-19?

Live vaccines can prevent unrelated infections and may temporarily protect against COVID-19

By Konstantin Chumakov[1,2], Christine S. Benn[3], Peter Aaby[4], Shyamasundaran Kottilil[5], Robert Gallo[2,5]

Science, 2020

- **BCG vaccine**
- **Measles/MMR vaccine**
- **Oral Polio Vaccine**

All have potential as ”stopgap” vaccines for COVID-19 and future pandemics

Lessons learned from BCG

BCG has effects that cannot be explained by prevention of tuberculosis:

- Numerous studies: 30-50% reductions in mortality
- Mechanistically shown to increase the immune response to other disease organisms
- Reduced viral load after viral challenge

Two propositions

- Vaccines do not only have specific effects
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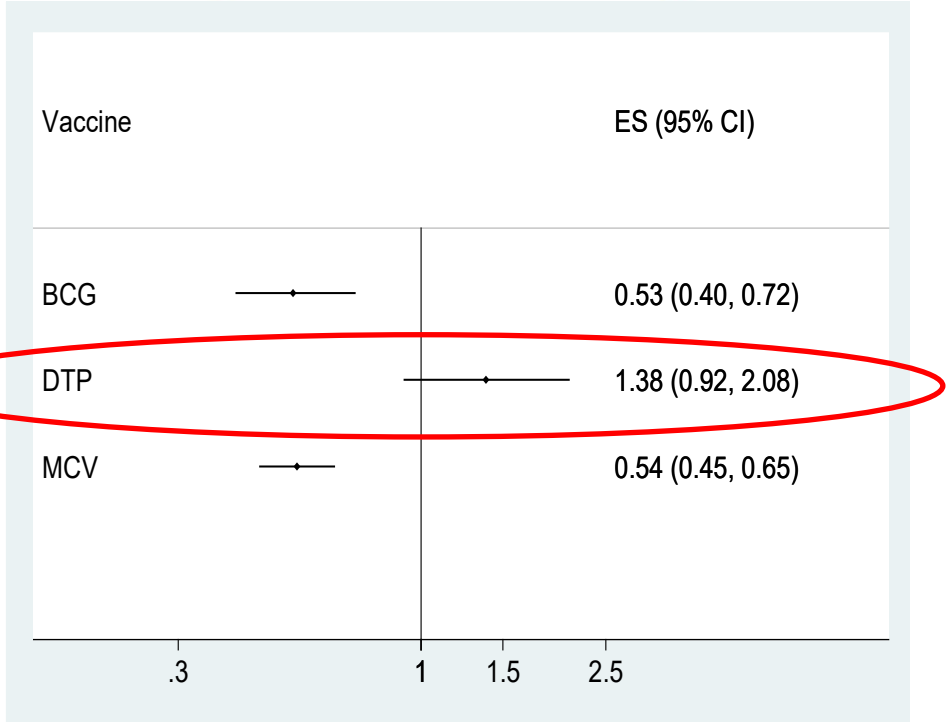


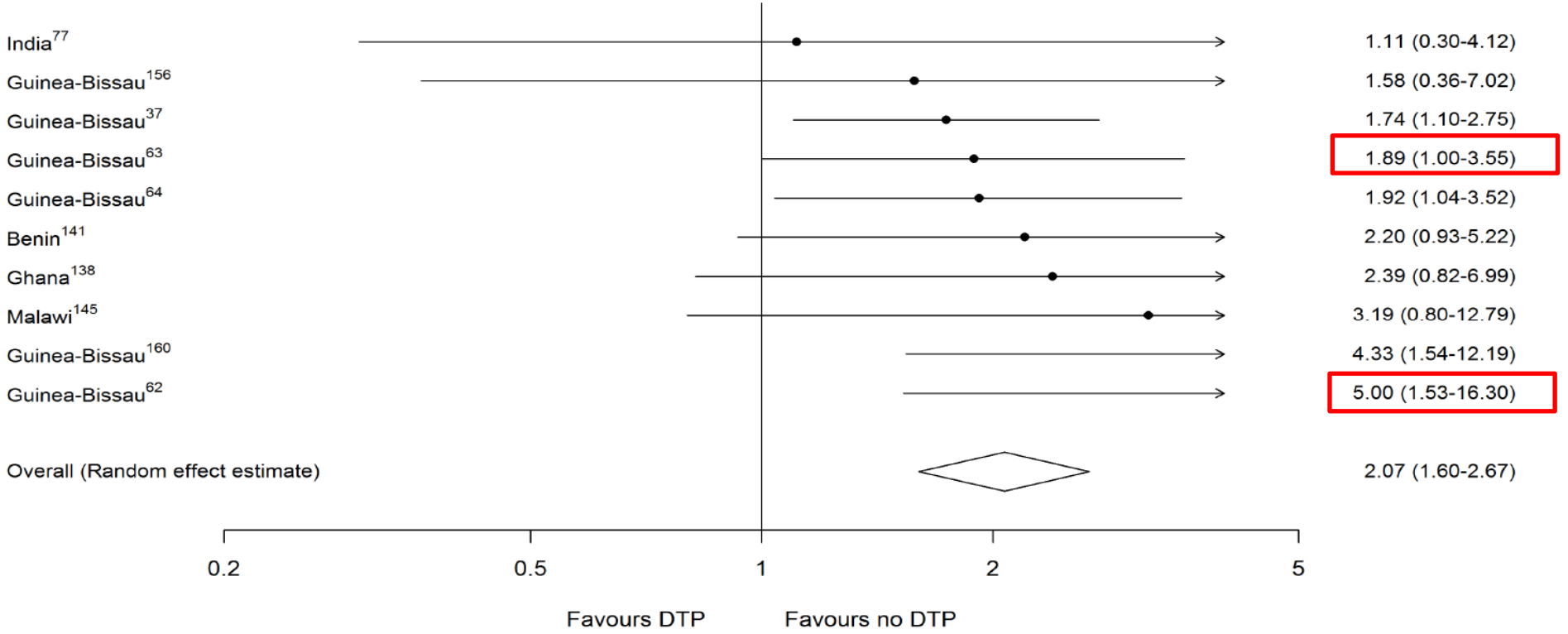
- Completely different effect on overall mortality of live BCG and measles vaccine vs. non-live diphtheria-tetanus-pertussis (DTP)-vaccine
- No bias can explain that

Higgins et al, BMJ 2016

The effect of being DTP-vaccinated

DTP versus no DTP – all children

Updated with two new studies

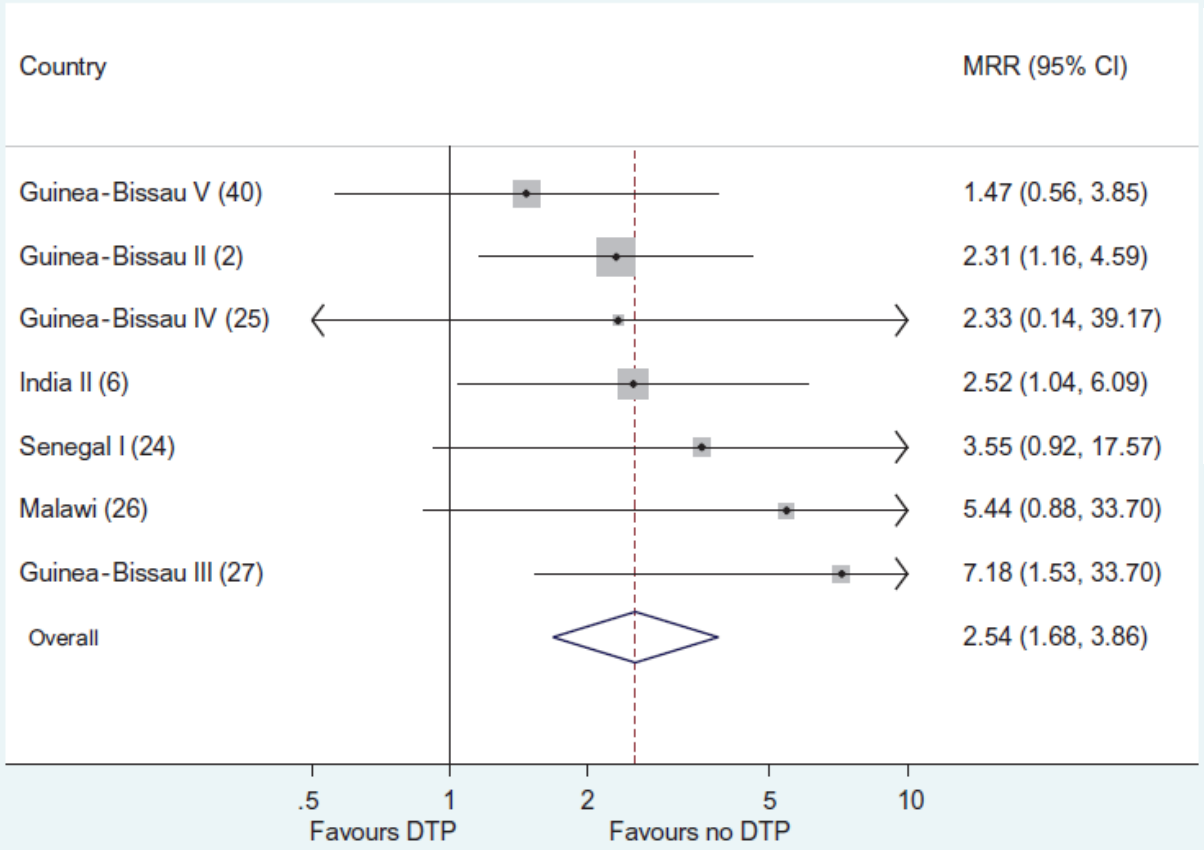


Meta-estimate: 2.07 (1.60-2.67)

Benn et al, Lancet Infect Dis 2020

Negative non-specific effects of DTP vaccine in females

DTP versus no DTP – females



DTP associated with 2.54 (1.68-3.86)-fold higher all-cause mortality in females, due to increased susceptibility to other infections.

Aaby et al, Trans R Soc Trop Med Hyg 2016

Clinical Infectious Diseases
MAJOR ARTICLE

Interacting, Nonspecific, Immunological Effects of Bacille Calmette-Guérin and Tetanus-diphtheria-pertussis Inactivated Polio Vaccinations: An Explorative, Randomized Trial

Bastiaan A. Blok,[1,2,3] L. Charlotte J. de Bree,[1,2,3] Dimitri A. Diavatopoulos,[4] Jeroen D. Langereis,[4] Leo A. B. Joosten,[1] Peter Aaby,[2] Reinout van Crevel,[1] Christine S. Benn,[2,3] and Mihai G. Netea[1]

Randomised trial of 75 females:

DTP induced innate tolerance:

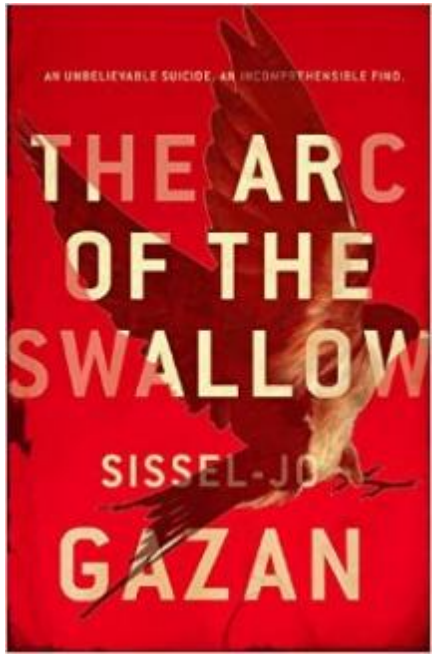
"Tdap ["DTP"] *vaccination led to short-term potentiation and* ***long-term repression of monocyte-derived cytokine responses****, and short-term as well as long-term repression of T-cell reactivity to unrelated pathogens"*

Blok et al, Clin Infect Dis 2020

Sissel-Jo Gazan: ”The arc of the swallow”

A scientific crime novel based on the our research:

Sissel-Jo in Guinea-Bissau, researching for the novel



Would somebody kill to stop a professor who proposes that vaccines have negative non-specific effects?

Lessons learned from DTP vaccine

- A vaccine that protects against a vaccine disease can have negative and sex-differential non-specific effects that makes it worse to get the vaccine than not to get it
- Girl: “Will I be healthier from taking this vaccine?” – No!
- We can do harm with vaccines if we do not take into account their non-specific effects

Our main research finding:
Non-specific effects of vaccines

Vaccines protect against the target disease, but have also important **non-specific effects (NSEs)** – affecting the susceptibility to other infectious diseases than the vaccine disease

- **Live vaccines** *(measles vaccine, BCG, smallpox vaccine, OPV)* have **beneficial NSEs**, protect against unrelated infections, and reduce all-cause morbidity and mortality

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The current paradigm for vaccines

- A **vaccine** is a biological preparation that improves immunity to a particular disease
- **Evaluation and monitoring** is based on (biomarkers for) the vaccine disease
- Effect on **overall health** is based on extrapolations

Vaccinology: time to change the paradigm?

Christine Stabell Benn, Ane B Fisker, Andreas Rieckmann, Signe Sørup, Peter Aaby

www.thelancet.com/infection **Published online July 6, 2020** **https://doi.org/10.1016/S1473-3099(19)30742-X**

Nature Milestones in Vaccines

700

900

940

980

1984

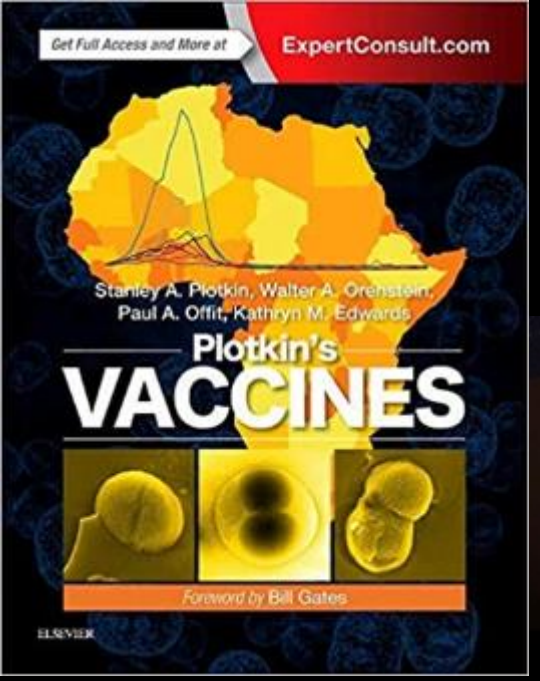
Milestone 13 1984

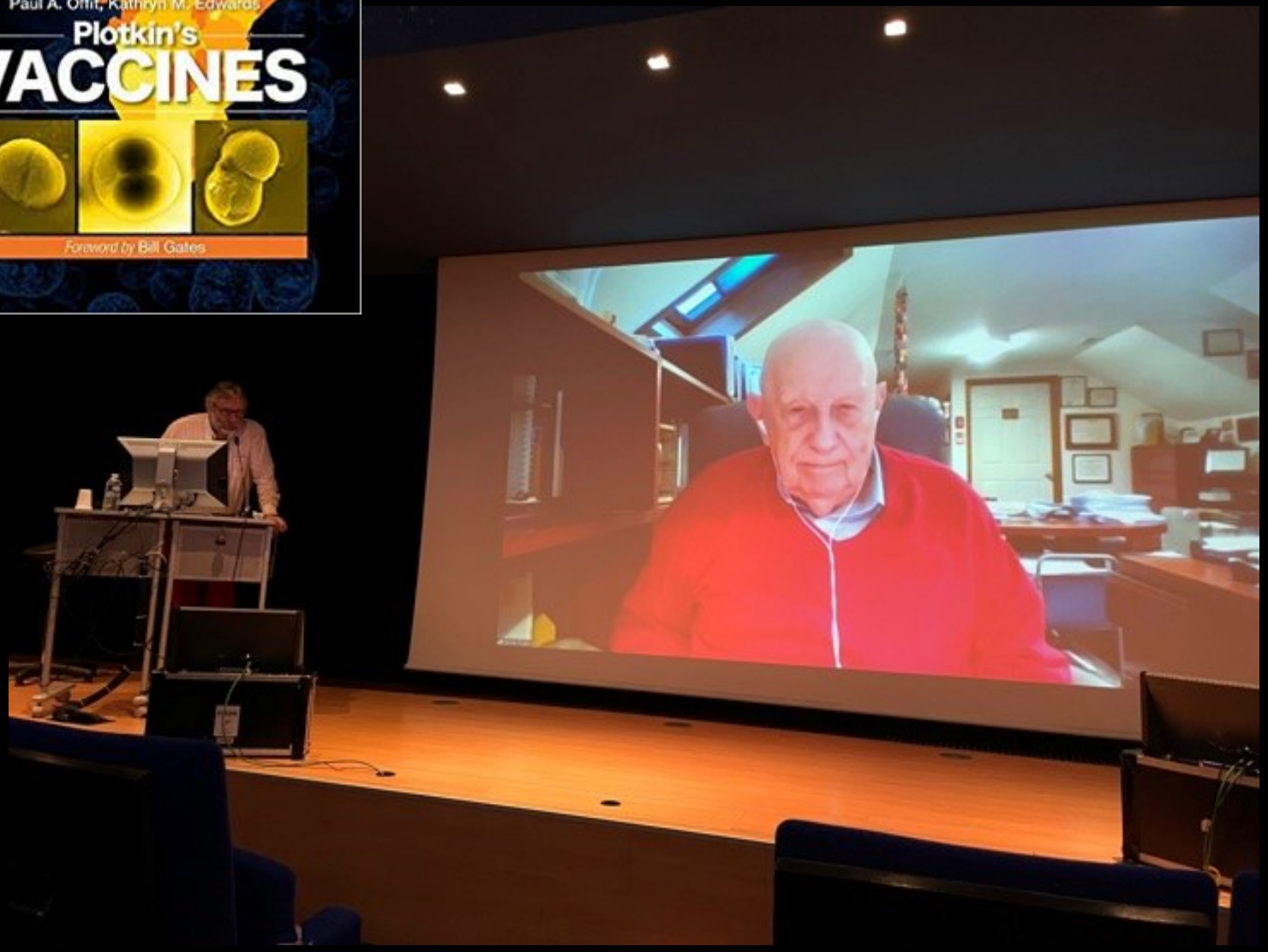
Another layer of protection

Studies by Peter Aaby and colleagues in the 1980s championed the idea of nonspecific effects of vaccines, expanding on observations throughout vaccine history that some live vaccines protect against infections other than those caused by the target pathogen. Read More

By Kirsty Minton

Credit: Royal Geographical Society / Alamy Stock Photo





Stanley Plotkin, 2021:

"In the history of science there were points where new concepts arise that changed our thinking, revolution of thoughts… In vaccinology, revolution was set in motion by Pasteur…. Now we have a new concept, that of non-specific effects, to which we owe Peter Aaby, Christine Benn, and Mihai Netea".

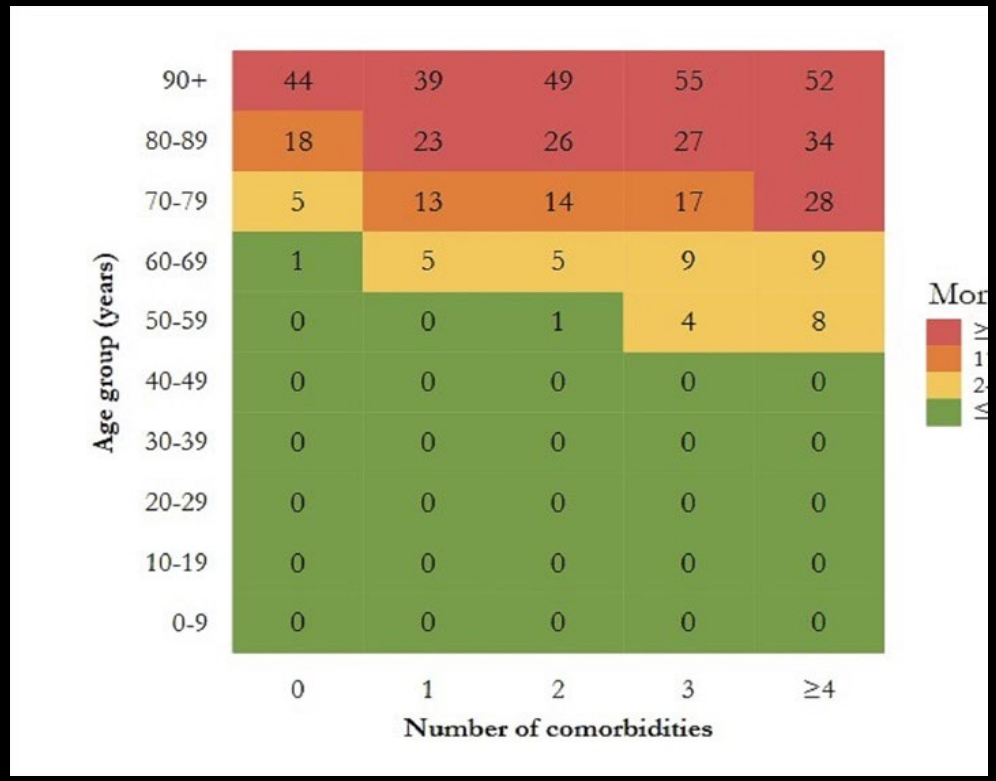
	Current phase 3 trials	Ideal phase 3 trials
”Placebo”	Some use another vaccine	Never use another vaccine (it may have non-specific effects)
Adverse events	Collected within a limited time frame (deaths/hospitalization for full duration) and assessed for plausibility.	All symptoms should be recorded for at least 6 months (everything is plausible)
Outcomes	Symptomatic COVID-infection.	Overall mortality and morbidity, e.g. all-cause consultation, hospitalisation, deaths
Duration of follow-up	Vaccinated control group once vaccine approved (average follow-up 4 months)	Follow-up of vaccinated and controls for at least 2 years
	Current post-marketing surveillance	Ideal post-marketing surveillance
Comparison groups	Obs. Vaccinated vs. unvaccinated; Before-after comparisons	Randomised trials Step-wedged roll-out
Safety	Reporting from GPs, citizens	Active follow-up through interviews/registers
Outcomes	”Plausible” adverse events	Overall mortality and morbidity, e.g. all-cause consultation, hospitalisation, deaths

Will I be healthier from taking a COVID-19 vaccine?

- **Benefits in terms of specific effects on mortality:**

  0-29-year-old: No
  30-49-year-old: Most likely not
  50-69-year-old: Maybe if co-morbidities
  70-79-year-old: Most likely, yes if co-morbidity
  80+-year-old: Yes

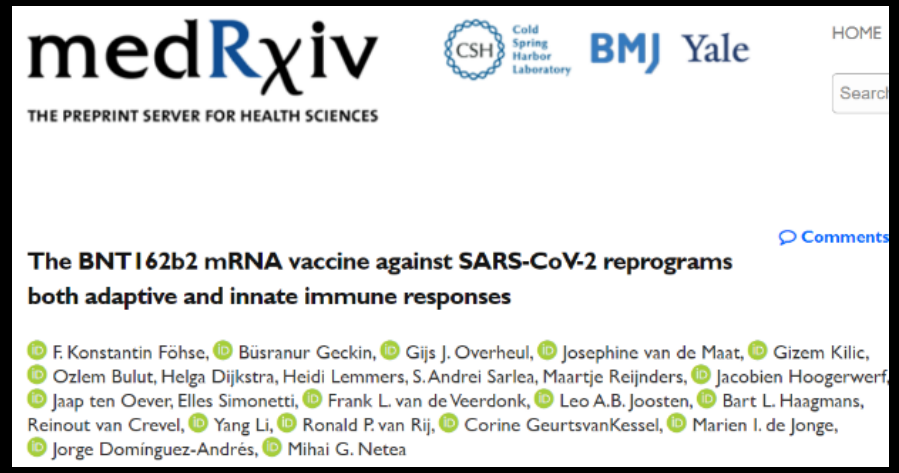
- **Rare but severe side effects?**
- **Non-specific effects?**



Reilev et al, Int J Epidemiol 2020

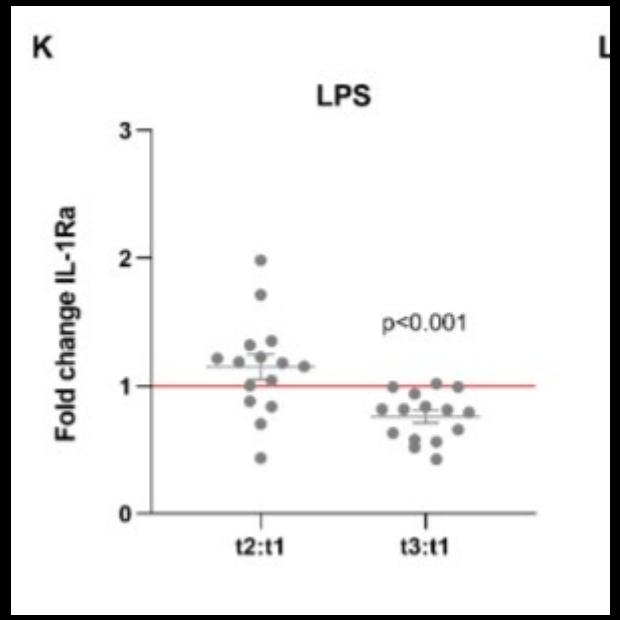
Protective effect against vaccine disease + **Non-specific effect** on other diseases = Effect on overall health

Preprint: Pfizer vaccine associate with innate immune tolerance

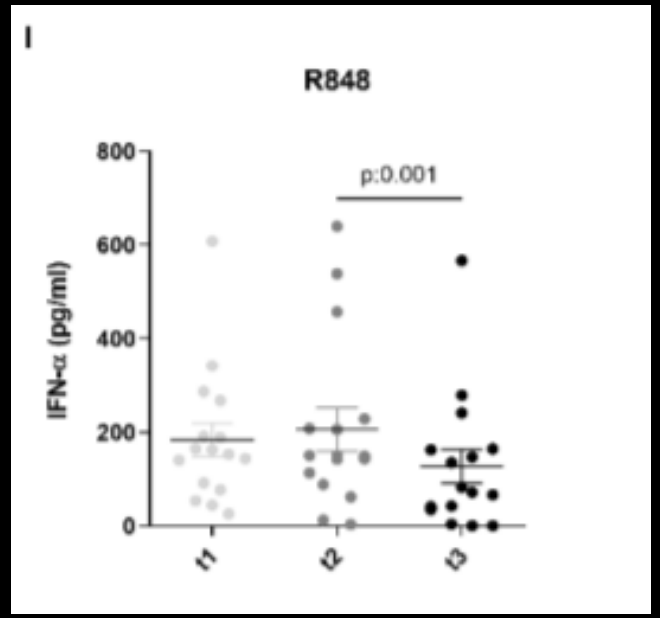


”The response of innate immune cells to TLR4 and TLR7/8 ligands [3 weeks after dose 1 and 2 weeks after dose 2] was lower after BNT162b2 vaccination…. In conclusion, the mRNA BNT162b2 vaccine induces complex functional reprogramming of innate immune responses, which should be considered in the development and use of this new class of vaccines”

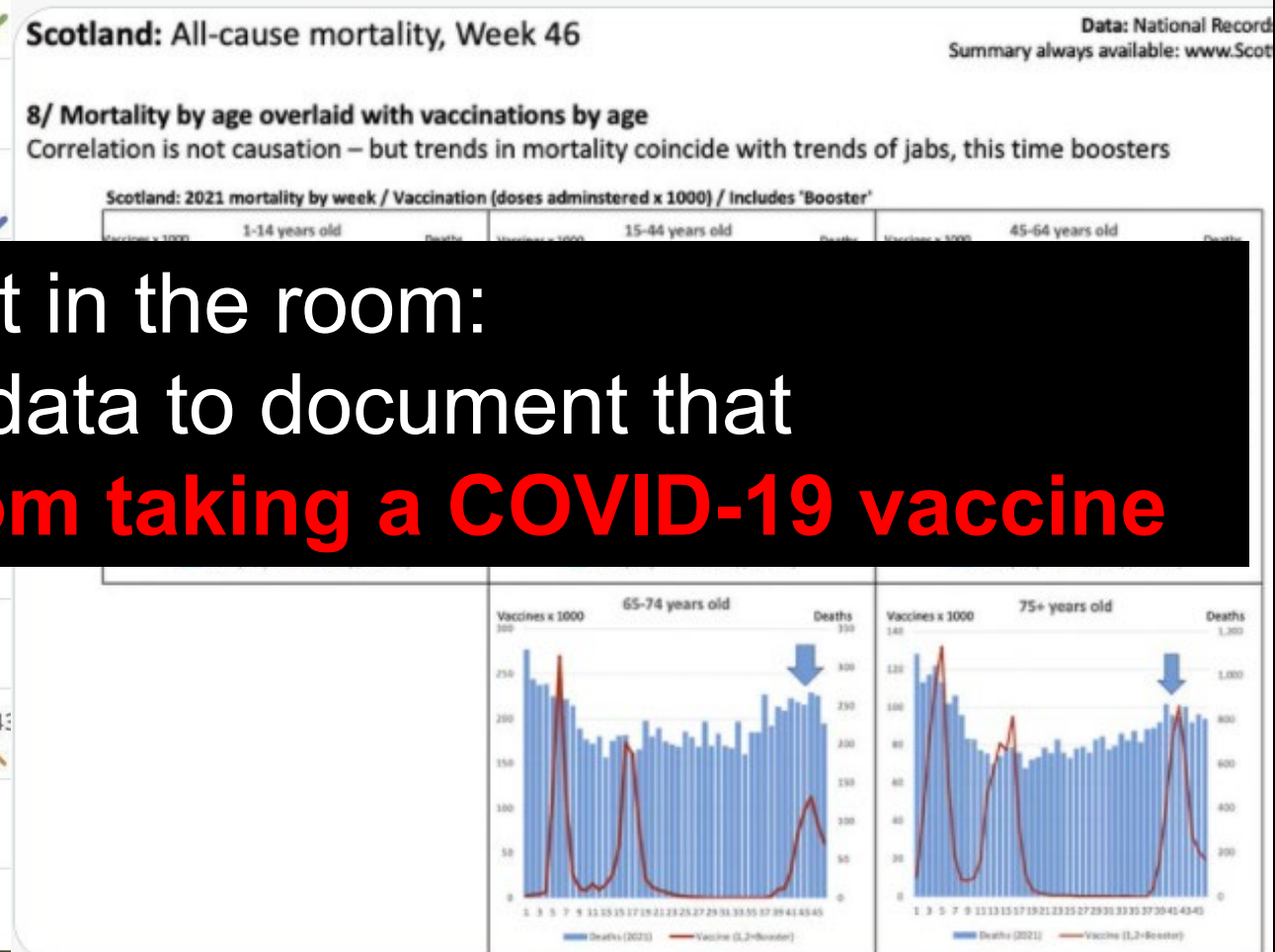
Bacterial ligand



Viral ligand



Some people claim:
COVID-19 vaccines may reduce COVID-19 deaths but increase the risk of all-cause mortalty



The elephant in the room:
We do not have the data to document that
YES, you will be healthier from taking a COVID-19 vaccine

What we learned from studying the overall health effects of vaccines

- Vaccines may have non-specific and sex-differential effects
- This is currently not taken into account when testing vaccines
- This omission has the potential to create breaches in vaccine confidence – rightly so, because we may be doing harm with some vaccines, despite the fact that they protect against the vaccine disease
- It is the health authorities' duty to document "no harm"
- We have to assess vaccines for their effect on overall health in both sexes
- For this we need epidemiologists to desgin clever phase 3 and phase 4 trials ☺

Thank you!

Bandim Health Project:
Peter Aaby
Ane Fisker
Signe Sørup
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Andreas Rieckmann
Amabelia Rodrigues
Cesario Martin
Isaquel da Silva

Nijmegen:
Mihai Netea
Bas Blok
Rob Arts
Charlotte de Bree
Simone Moorlag
Mike Berendsen
Pauli de Bles

Mothers and children in Guinea-Bissau

OPTIMMUNIZE 2022

Optimizing the beneficial non-specific effects (NSEs) of vaccines

April 19-21, 2022

Danish Institute for Advanced Study
Odense, Denmark