Why do newborns die?
What we can do about it:
Shift focus from pathogen to host

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Professor of Pediatric Infectious Diseases

Perth Children's Hospital, UWA

Telethon Kids Institute

Telethon Kids Institute acknowledges Aboriginal and Torres Strait Islander people as the Traditional Custodians of the land and waters of Australia.

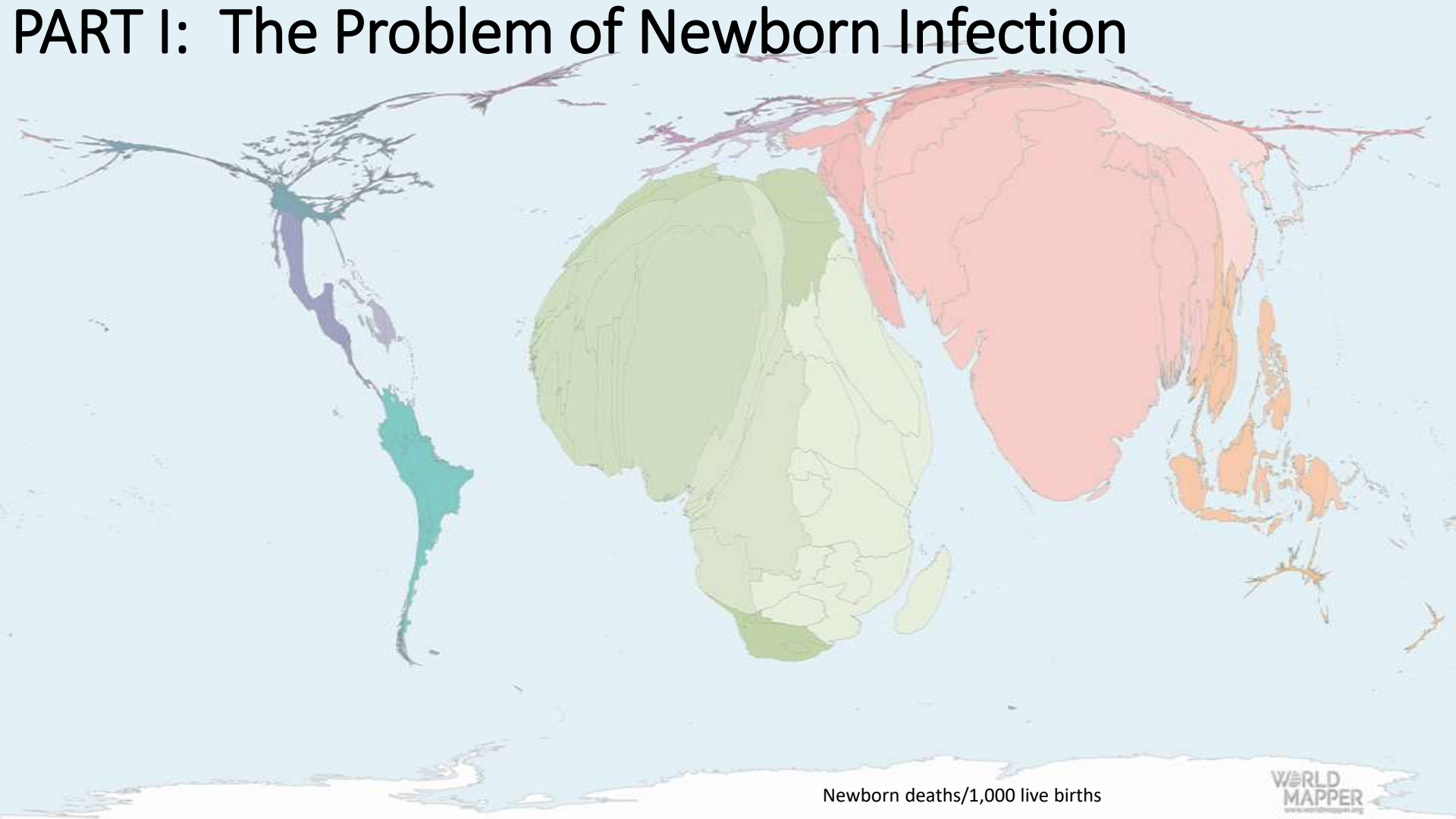
We also acknowledge the Nyoongar Wadjuk, their people and their land upon which this Institute is located and seek their wisdom in our work to improve the health and development of all children.

What I will present today:

- PART I: The problem (newborn infection)
- PART II: The *main* problem (existing dogma)
- Part III: The solution (already exists!!!)
- Part IV: The *main* solution (switch focus to host)

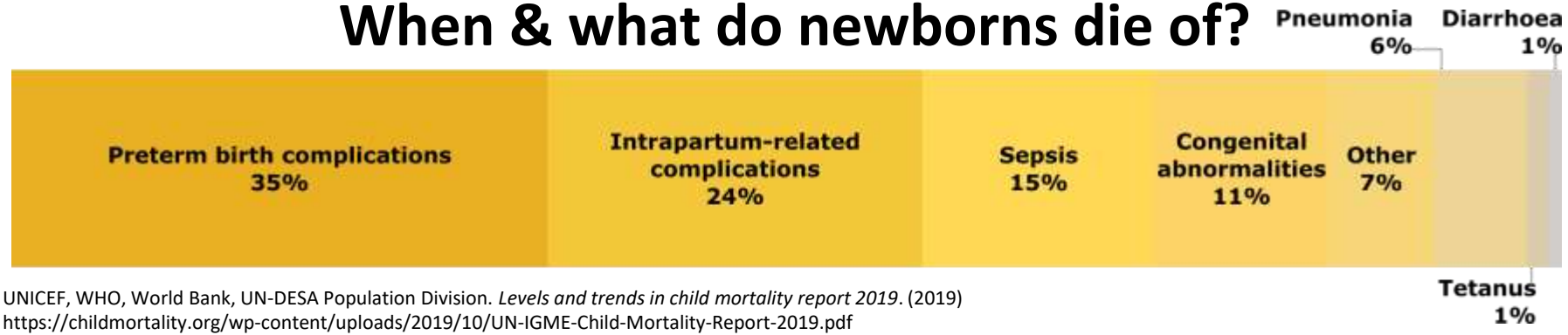
PART I: The Problem of Newborn Infection

PART I: The Problem of Newborn Infection



PART II: The main problem (existing dogma)

When & what do newborns die of?



UNICEF, WHO, World Bank, UN-DESA Population Division. *Levels and trends in child mortality report 2019*. (2019)
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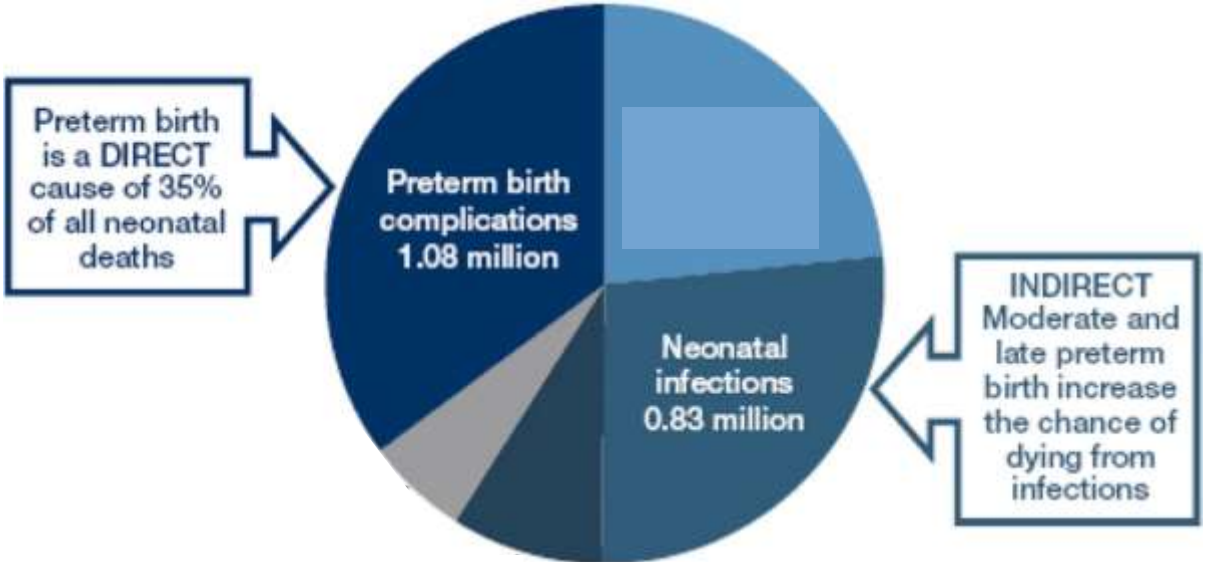


Preterm birth is a risk factor for neonatal and postneonatal deaths

At least 50% of all neonatal deaths are preterm

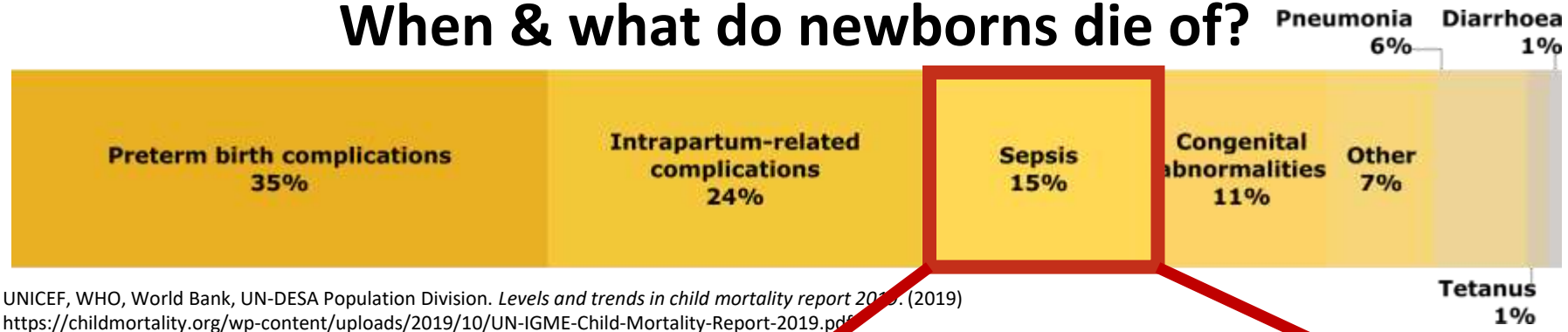
BORN STRONG INITIATIVE

EMPOWERING MOTHERS
BOOSTING BABY'S
IMMUNITY

Visit us at born-strong.org

PART II: The main problem (existing dogma)

When & what do newborns die of?



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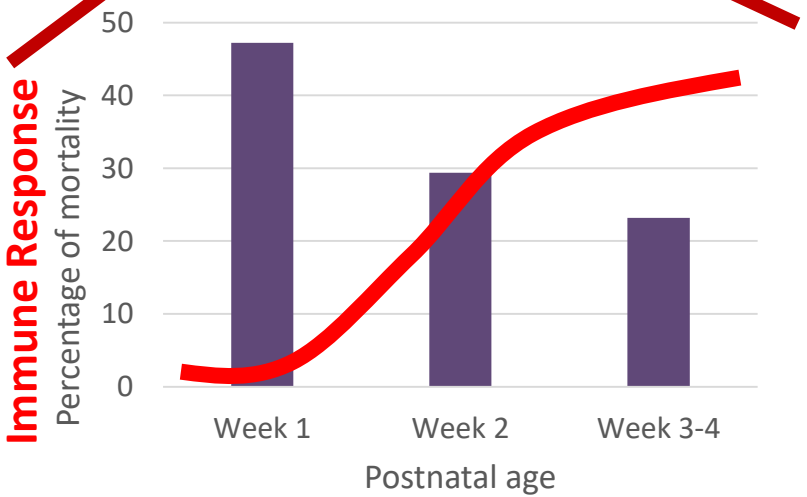
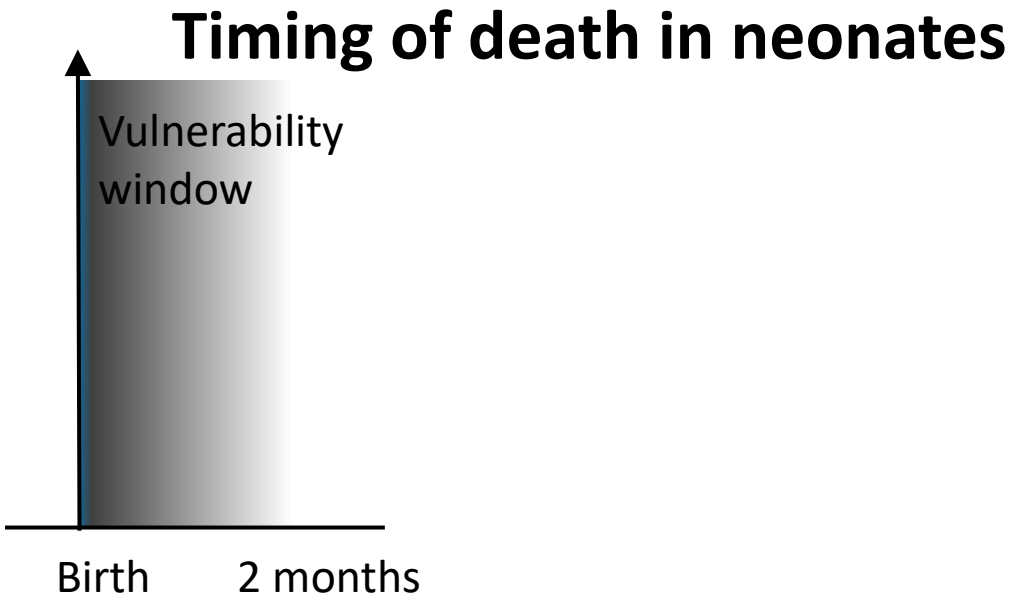


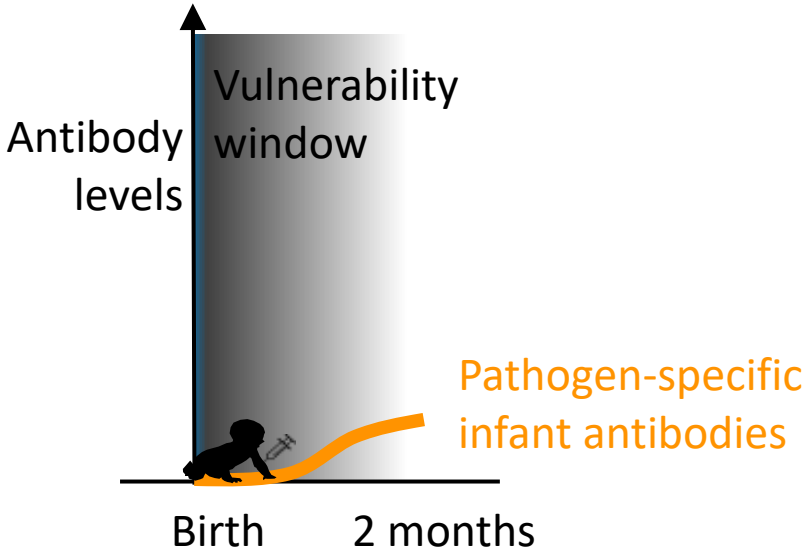
Adapted from: Sankar, M., Natarajan, C., Das, R. *et al.* When do newborns die? A systematic review of timing of overall and cause-specific neonatal deaths in developing countries. *J Perinatol* **36,** S1–S11 (2016). https://doi.org/10.1038/jp.2016.27

PART II: The main problem (existing dogma)



Science **368**, 612–615 (2020)

PART II: The main problem (existing dogma)



Science **368**, 612–615 (2020)

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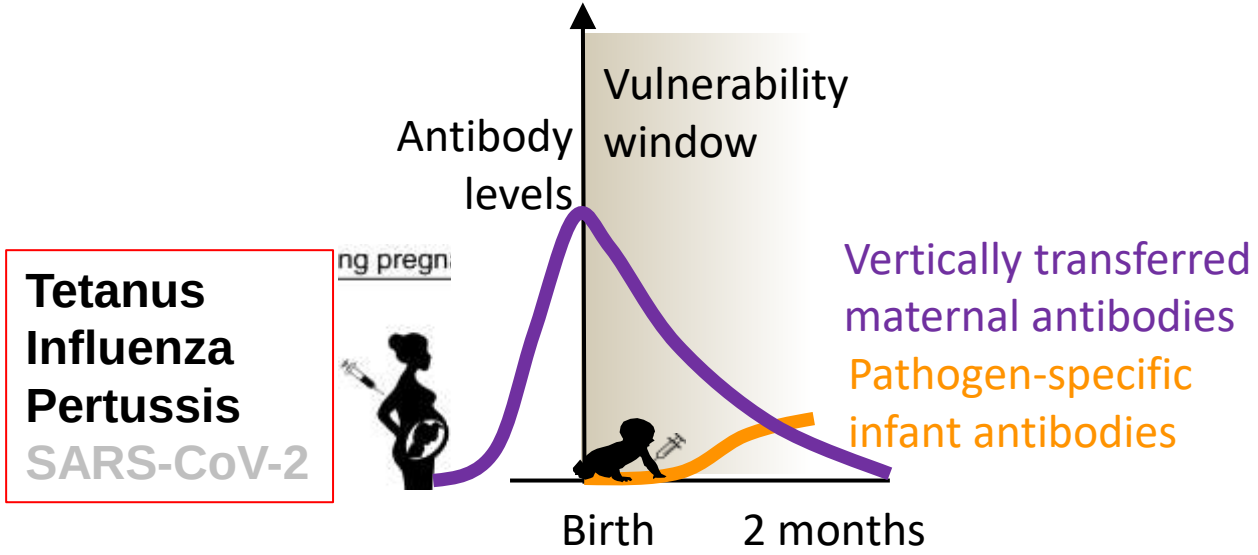
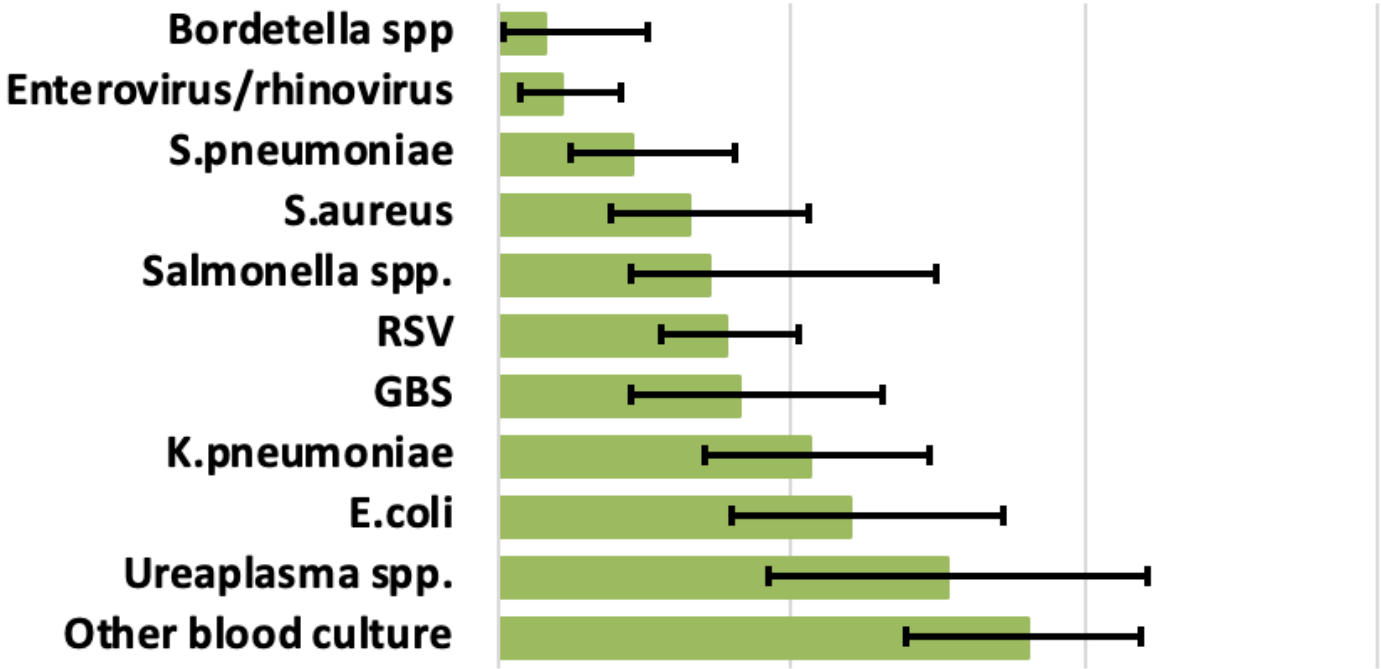


Science **368**, 612–615 (2020)

PART II: The main problem (existing dogma)

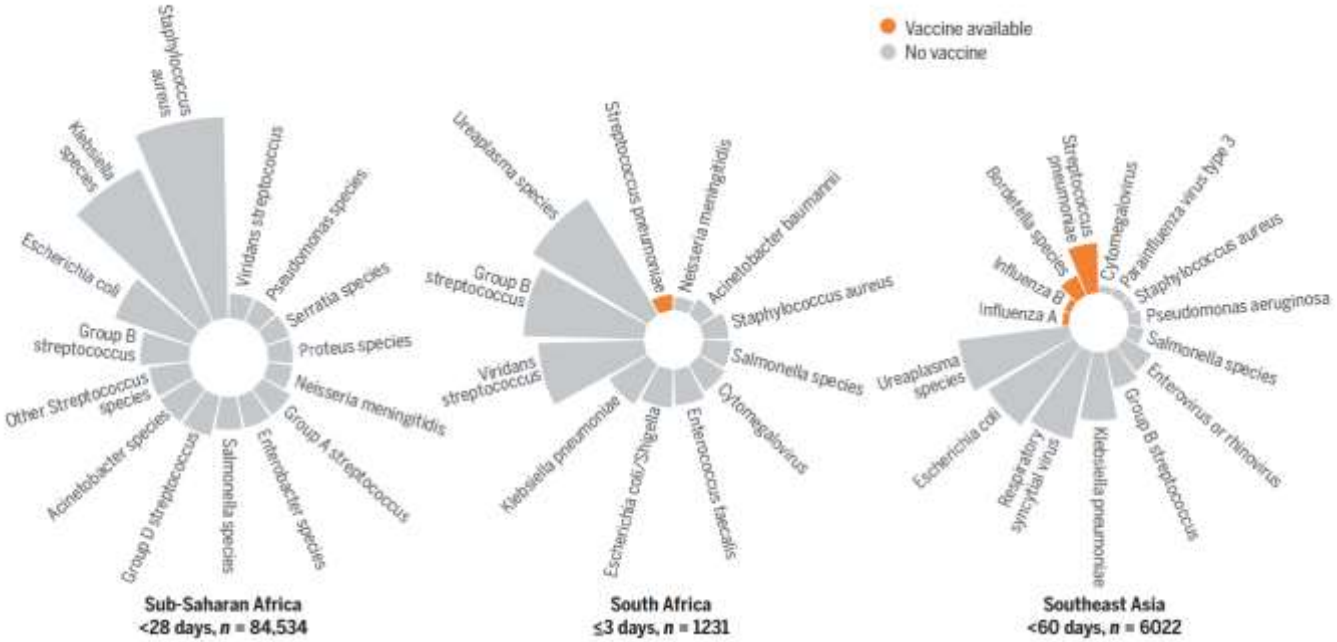
Causes of severe 'infectious disease' in neonates



>70% had NO PATHOGEN identified

Saha S et al. Lancet 2018; S0140-6736(18)31432-6

PART II: The main problem (existing dogma)



The ‘one vaccine for one bug’ approach will *not* suffice

Kollmann, T. R., A. Marchant, and S. S. Way. 2020. Vaccination strategies to enhance immunity in neonates. *Science* 368: 612-615.

PART II: The main problem (existing dogma)

Existing approach ***not*** working!!!
- misses actual cause of death (how does sepsis kill?)
- misses timing & many/most pathogens

SCIENCE | REVIEW

Vaccination Strategies to Enhance Immunity in Newborn Infants

Tobias R. Kollmann[1*†], Arnaud Marchant[2*†], Sing Sing Way[3†]

PART III: The solution (existing vaccines)

Nelly Amenyogbe

Byron Brook

Peter Aaby

Christine Stabell Benn

Acknowledgements: it takes a village

PART III: The solution (existing vaccines)

Nov 2020

"non-specific effects"

"heterologous effects"

"off-target effects"

"secondary effects"

"pathogen-agnostic effects"

Vaccinology: time to change the paradigm?

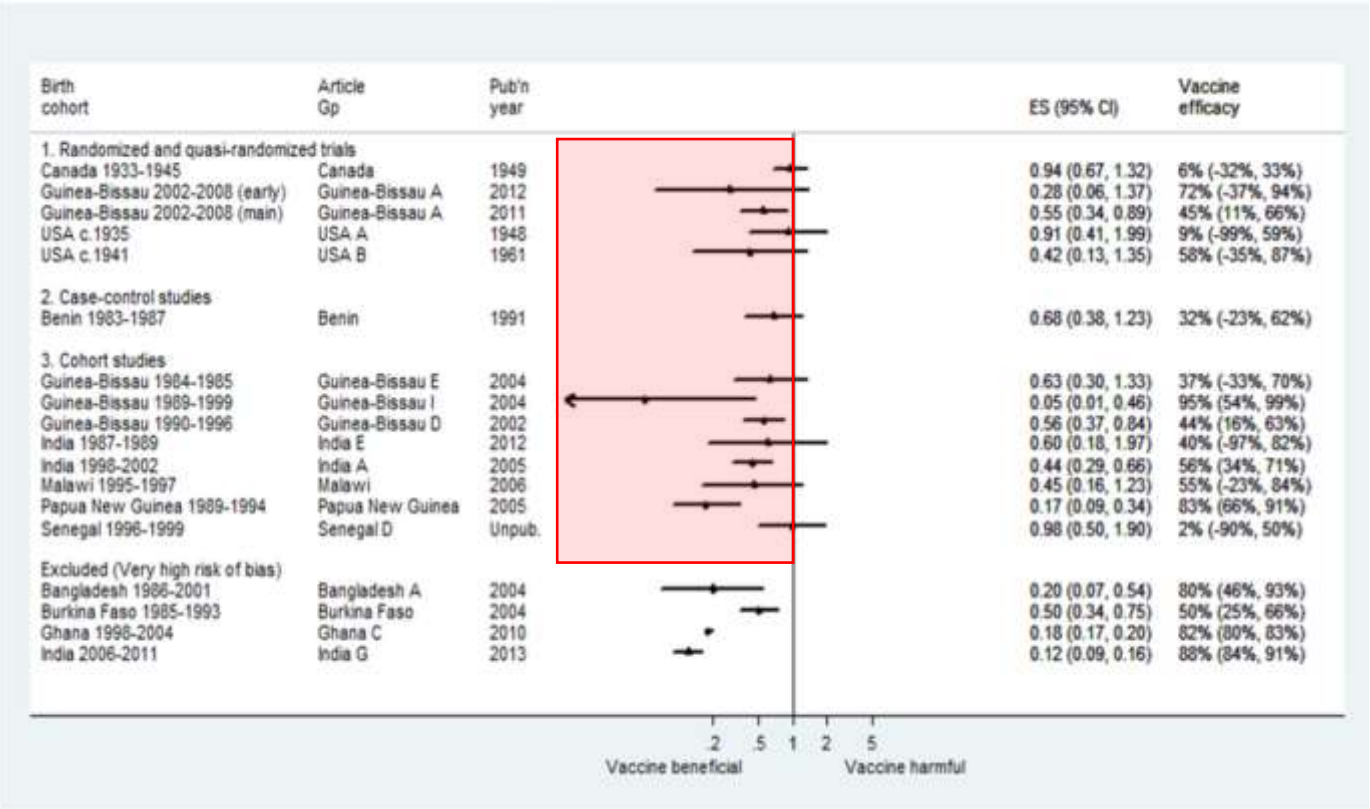
Christine Stabell Benn, Ane B Fisker, Andreas Rieckmann, Signe Sørup, Peter Aaby

THE LANCET
Infectious Diseases

www.thelancet.com/infection **Published online July 6, 2020**

PART III: The solution (existing vaccines)

Newborn immunization: pathogen-agnostic effects



WHO review concludes:

Neonatal BCG reduces mortality far beyond TB.

Higgins JPT, Systematic review of the non-specific effects of BCG, DTP and measles containing vaccines. Report to WHO, 13 March 2013

PART III: The solution (existing vaccines)

Newborn immunization: pathogen-agnostic effects

Randomized Trial of BCG Vaccination at Birth to Low-Birth-Weight Children: Beneficial Nonspecific Effects in the Neonatal Period?

Peter Aaby,[1,2] Adam Roth,[3,6] Henrik Ravn,[3] Bitiguida Mutna Napirna,[2,a] Amabelia Rodrigues,[1] Ida Maria Lisse,[4] Lone Stensballe,[3] Birgitte Rode Diness,[1] Karen Rokkedal Lausch,[1] Najaaraq Lund,[1] Sofie Biering-Sørensen,[1] Hilton Whittle,[5] and Christine Stabell Benn[1,3]

- Mortality rate of BCG group 45% less than unvaccinated infants
- 53% lower for very low birth weight infants
- Starts to impact at day 3 of life, i.e. just days after vaccination

Aaby P *et al.* *JID* 204:245 (2011)
PMID: 21673035

PART III: The solution (existing vaccines)

Newborn immunization: pathogen-agnostic effects

1 FEBRUARY

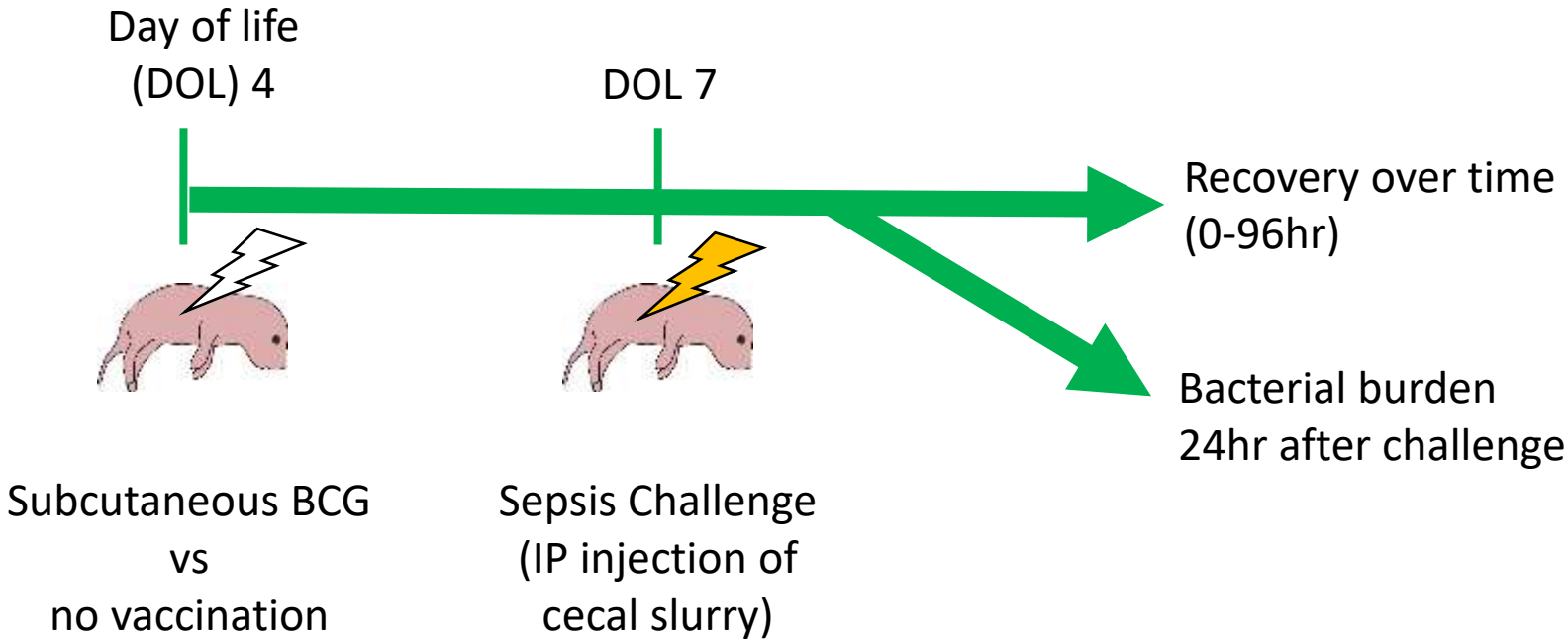
Correspondence

PMID: 22147789

Non-specific effects of BCG?

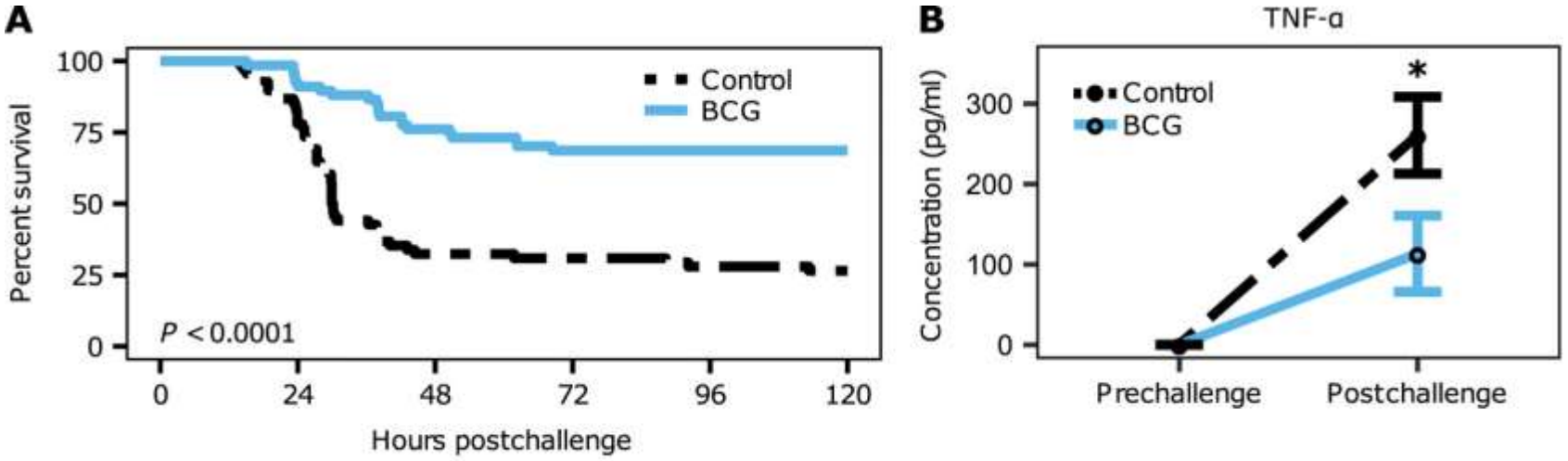
To the Editor—We would like to comment on the data presented by Aaby et al regarding their randomized trial of BCG in low-birth-weight children [1]. in the supplementary table available online, is that the apparent reduction in mortality occurred *entirely* in the first 21 days of life. Indeed, it is stated that the tendency appeared "already during the first 3 days after BCG vaccination."

In terms of mechanism, the authors suggest that "BCG might prepare the immune system to mount an effective response to infectious pathogens and therefore enhance survival." It seems unlikely that an immunological mechanism could explain so rapid an impact on mortality.


Day of life
(DOL) 4
DOL 7
Recovery over time
(0-96hr)
Bacterial burden
24hr after challenge
Subcutaneous BCG
vs
no vaccination
Sepsis Challenge
(IP injection of
cecal slurry)

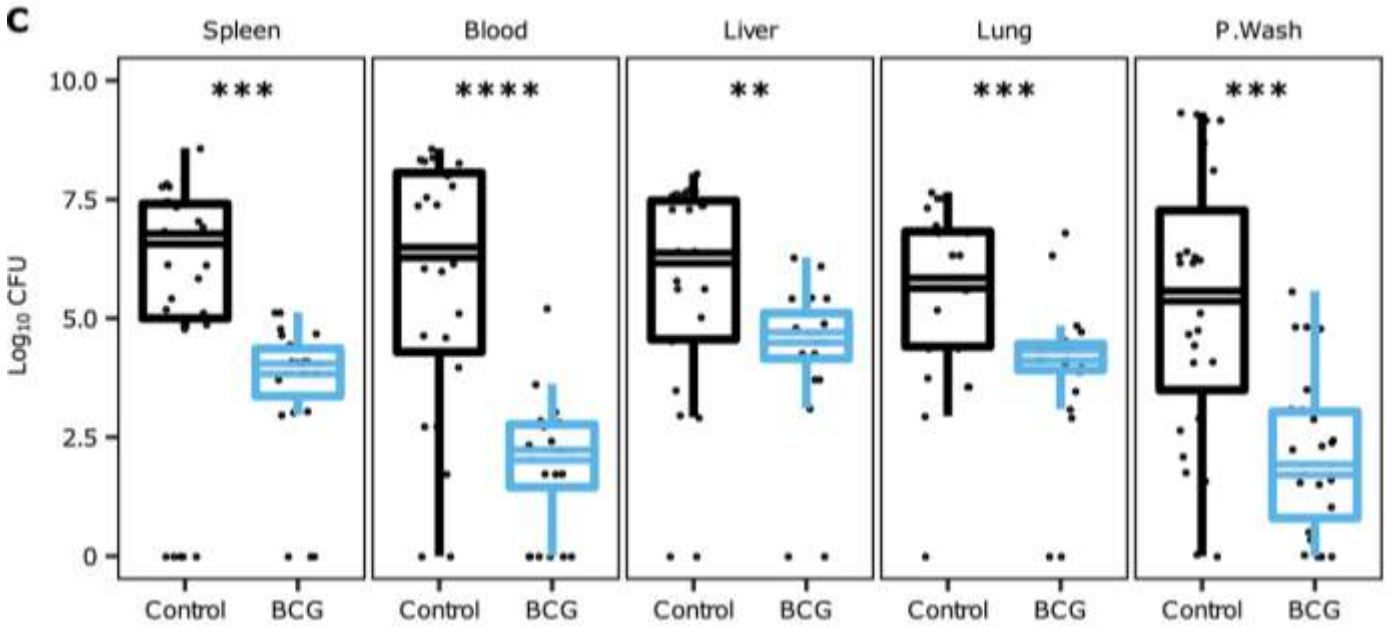
BCG protects newborn mice from septic death

- BCG vaccination protected newborn mice from septic death
- BCG-vaccinated mice had lower levels of pro-inflammatory plasma cytokines



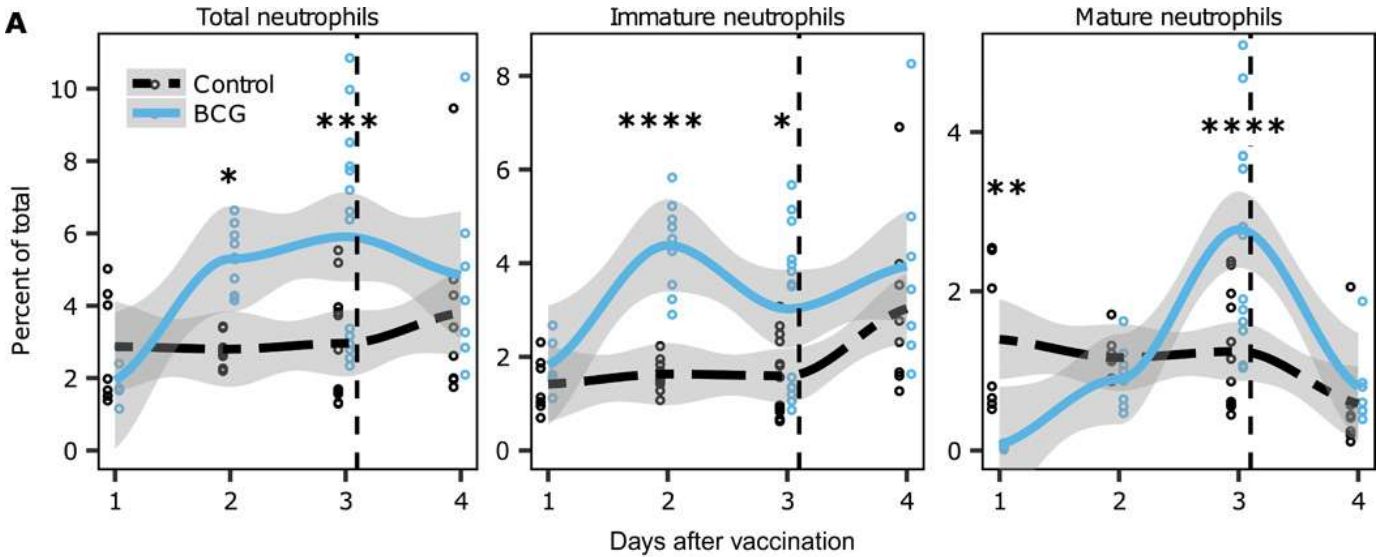
BCG-vaccination enhanced bacterial clearance

Bacterial burden assessed one day post challenge



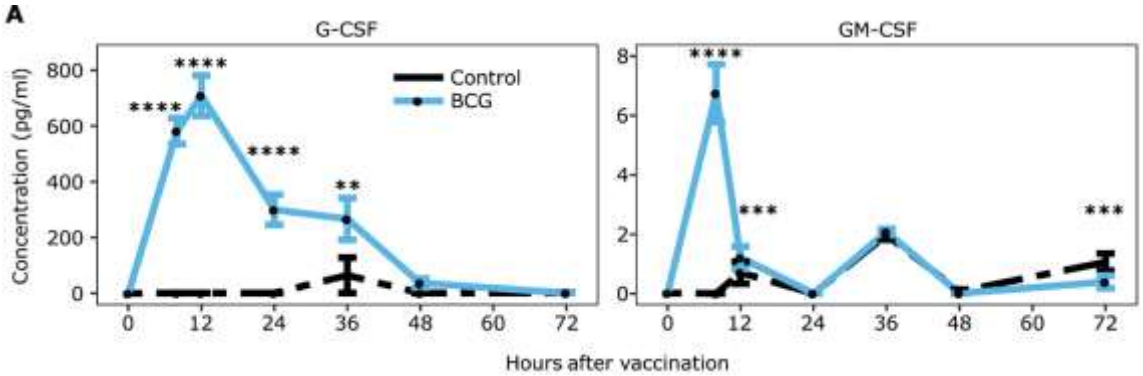
BCG vaccination increased the frequency of neutrophils in the spleen

Splenic pools of mature neutrophils doubled within 3 days of vaccination and were depleted after septic challenge

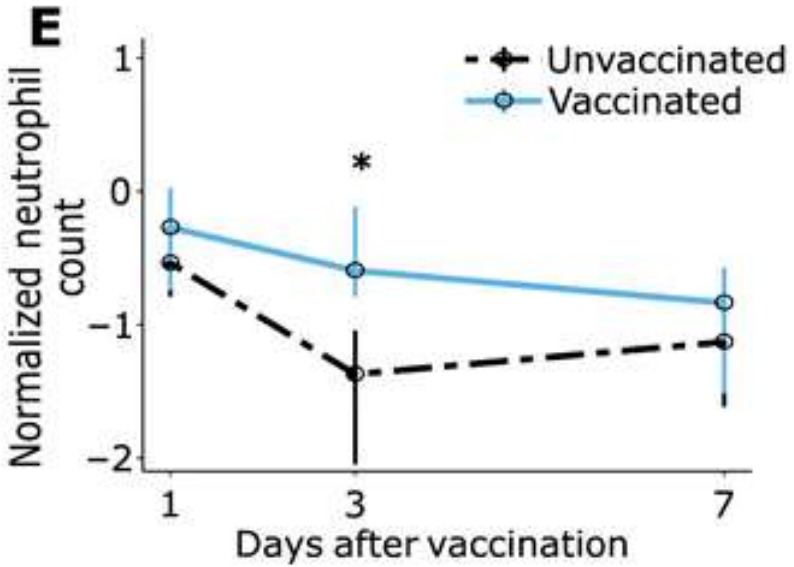


Emergency Granulopoesis: the responsible mechanism

Levels of G-CSF rapidly increased following BCG vaccination



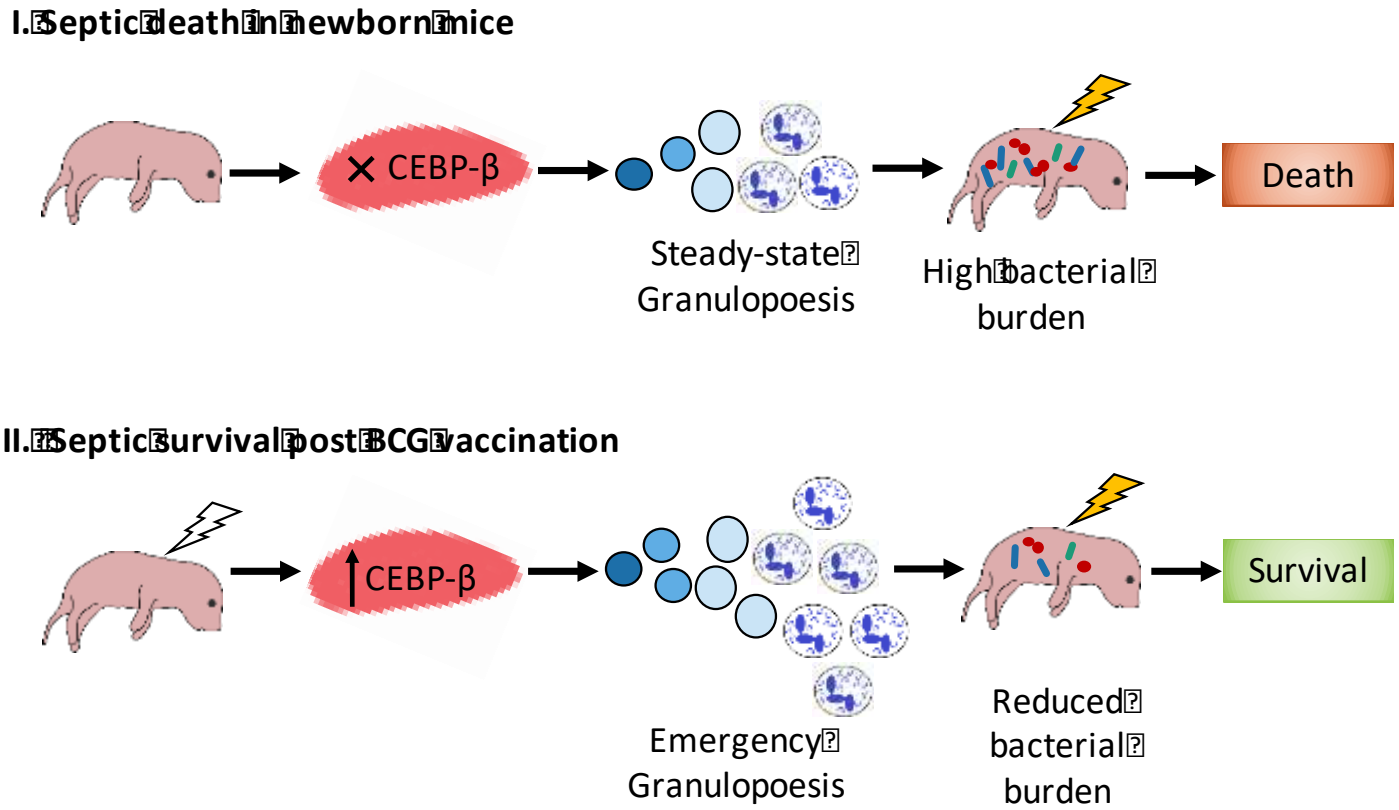
A slower decline in mature neutrophils in BCG-vaccinated newborns



Mature neutrophil counts in Gambian newborns over the first week of life did not decline over the first three days of life compared to unvaccinated newborns

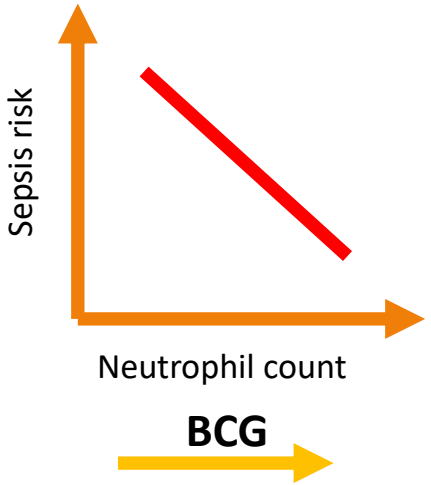
epic

The underlying mechanism: current understanding



PART III: The solution (existing vaccines)

Newborn immunization: pathogen-agnostic effects



In newborns BCG vaccination induces emergency granulopoiesis within **1-3 days** of administration

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

SEPSIS

Brook *et al.*, *Sci. Transl. Med.* **12**, eaax4517 (2020) 6 May 2020

BCG vaccination–induced emergency granulopoiesis provides rapid protection from neonatal sepsis

Byron Brook[1], Danny J. Harbeson[1], Casey P. Shannon[2,3], Bing Cai[4], Daniel He[1,2,3], Rym Ben-Othman[4], Freddy Francis[1], Joe Huang[4], Natallia Varankovich[4], Aaron Liu[1], Winnie Bao[4], Morten Bjerregaard-Andersen[5,6,7], Frederik Schaltz-Buchholzer[5,6,8], Lilica Sanca[5], Christian N. Golding[5,6], Kristina Lindberg Larsen[5,6], Ofer Levy[9,10,11], Beate Kampmann[12,13], The EPIC Consortium*, Rusung Tan[14], Adrian Charles[14], James L. Wynn[15], Frank Shann[16], Peter Aaby[5], Christine S. Benn[5,6,8], Scott J. Tebbutt[2,3,17], Tobias R. Kollmann[1,4,18†‡], Nelly Amenyogbe[1,18†‡]

PART III: The solution (existing vaccines)

BCG-induced non-specific effects on heterologous infectious disease in Ugandan neonates: an investigator-blind randomised controlled trial

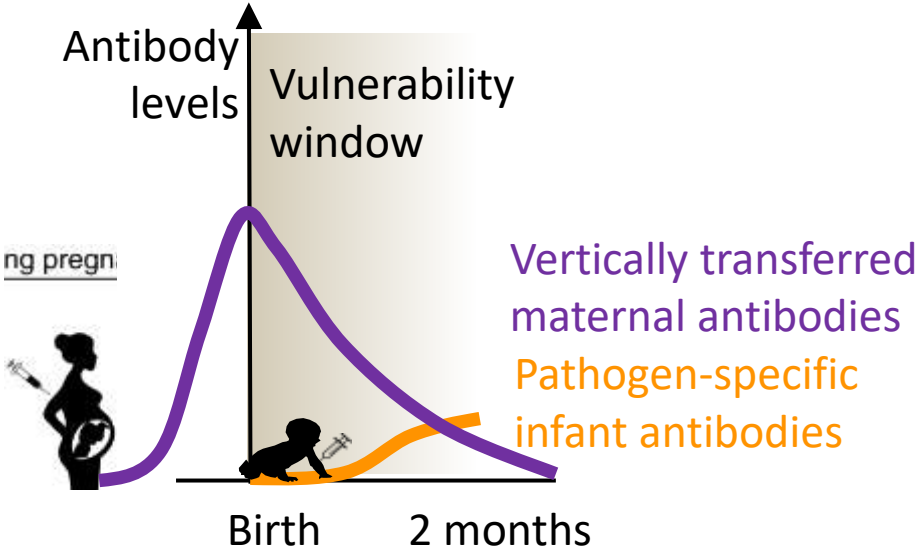
*Sarah Prentice, Beatrice Nassanga, Emily L Webb, Florence Akello, Fred Kiwudhu, Hellen Akurut, Alison M Elliott, Rob J W Arts, Mihai G Netea, Hazel M Dockrell, Stephen Cose, for The Delayed BCG Study Team**

www.thelancet.com/infection **Published online February 17, 2021** **https://doi.org/10.1016/S1473-3099(20)30653-8**

BCG: Mystery solved?

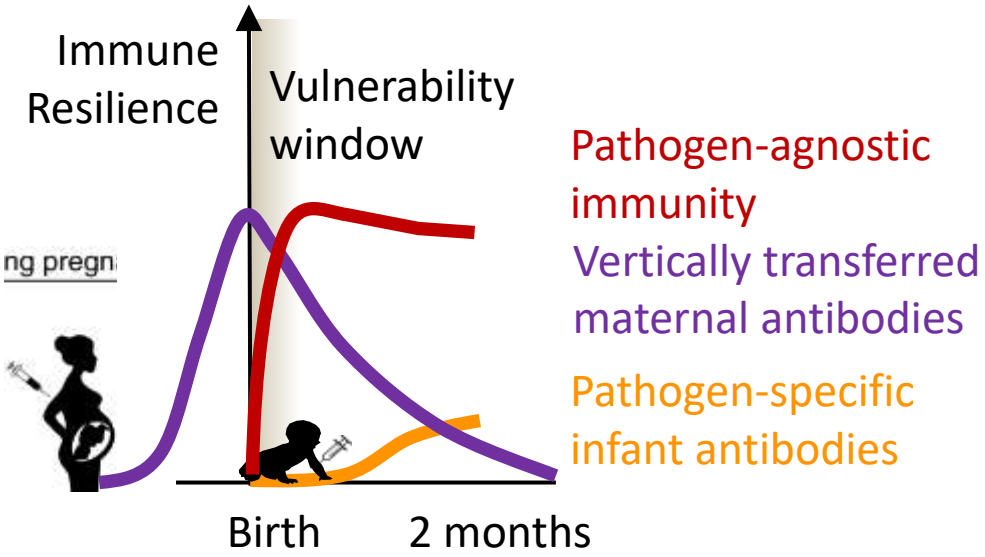
- The *pathogen-agnostic* effects of vaccines are slowly being recognized
- Many questions remain unanswered for the BCG vaccine outside the newborn period, and *may* help reduce the risk for other infections like malaria, respiratory disease incl. COVID
- Importantly, BCG doesn't always work. And to understand why, we need to understand **immune ontogeny**

PART III: The solution (existing vaccines)

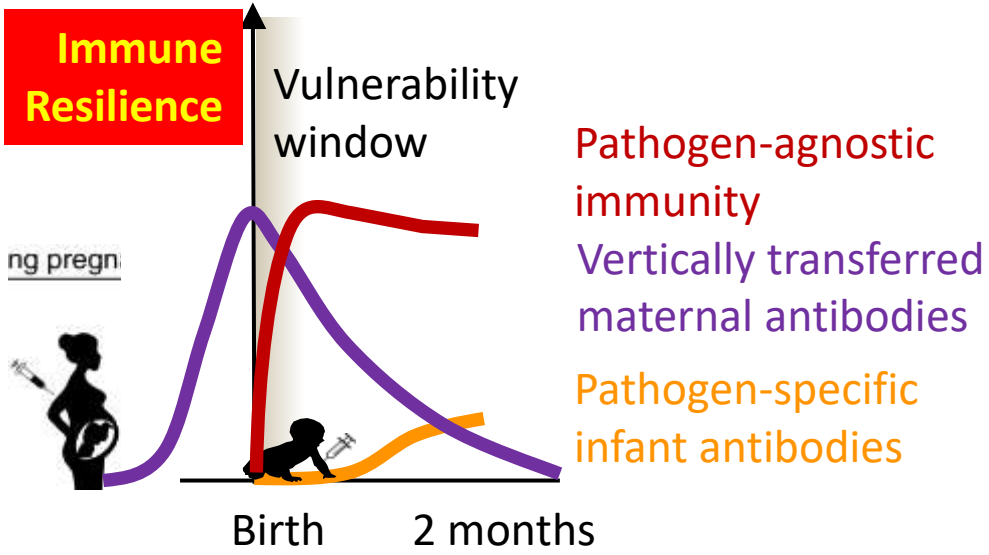


Science **368**, 612–615 (2020)

PART III: The solution (existing vaccines)

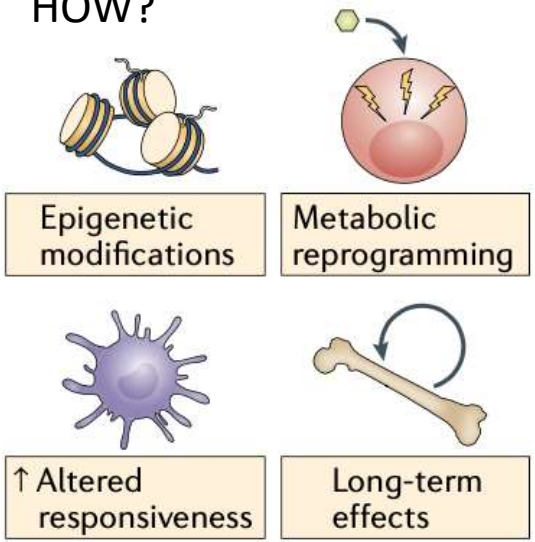


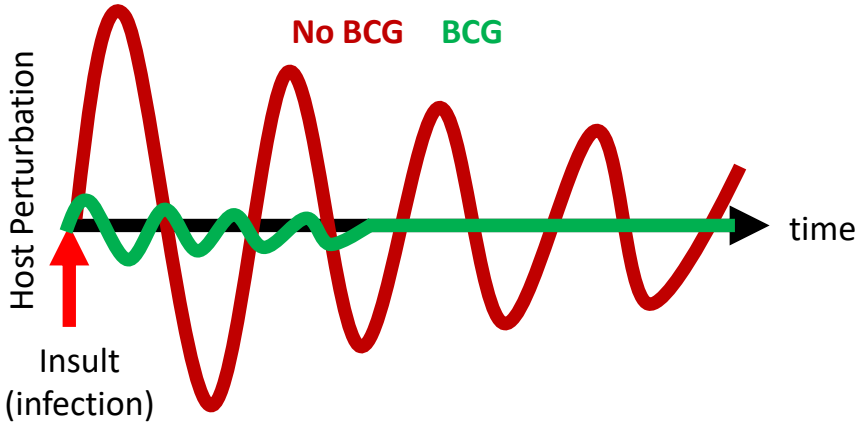
PART IV: The *main* solution (switch focus to host)



PART IV: The *main* solution (switch focus to host)

HOW?

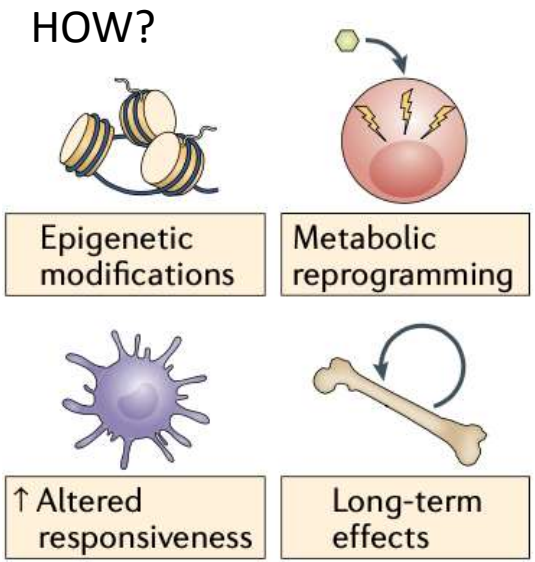


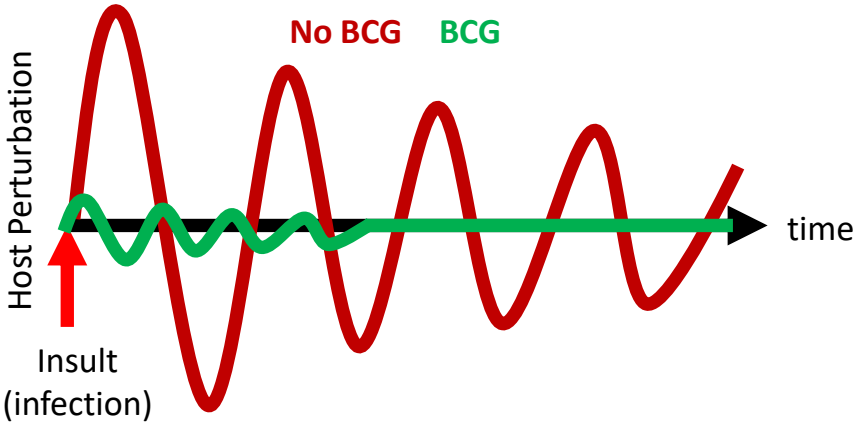


Increased immune resilience
(not simply *more*)
= **reduced**
Infectious **disease**
Inflammatory **disease**

Nature Reviews Immunology **20**, 375–388(2020)

PART IV: The *main* solution (switch focus to host)





Nature Reviews Immunology **20**, 375–388(2020)

What I presented today:

- The **problem** of newborn infection remains largely unchecked
- The ***main*** **problem** is our existing (dogmatic) approach
- Part of the **solution** is to harness pathogen-agnostic, immune modulatory effects (inlc. of existing vaccines)
- The ***main*** **solution** is to switch our focus from pathogen to the host

Thank You

tkollm@mac.com

Resilience/Fitness is dictated by host metabolism

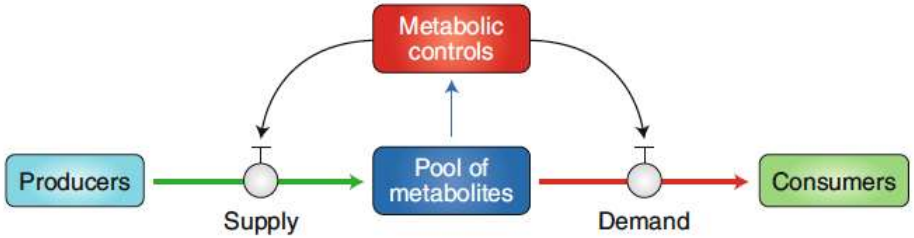
nature metabolism

REVIEW ARTICLE

https://doi.org/10.1038/s42255-019-0118-8

Control strategies in systemic metabolism

Jessica Ye and Ruslan Medzhitov*



Stock in-flow:
gluconeogenesis

Stock out-flow:
glycolysis

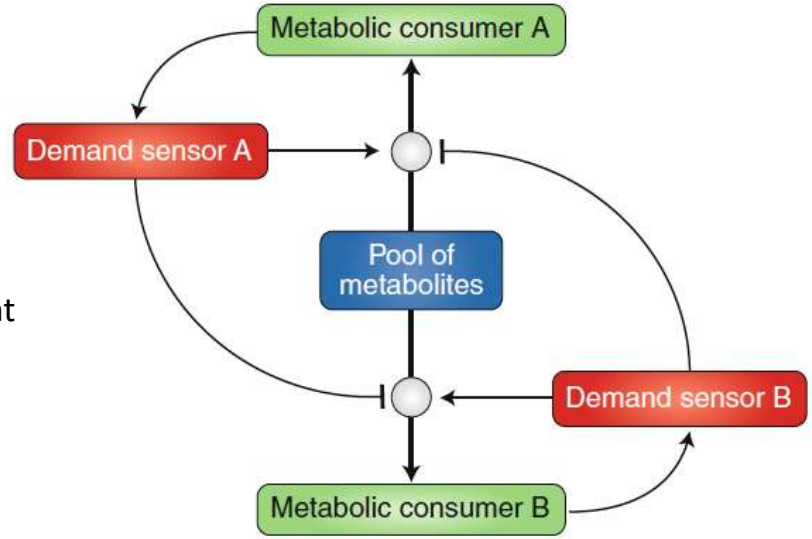
Competing Demands

When resources are scarce, demands must be prioritized.

Prioritization is hard-wired:
- Higher affinity for glucose in the brain
- Higher affinity for fatty acids in the heart

Prioritization is context-dependent:
- Skeletal muscle gets a higher priority during fight or flight
- Immune system a higher priority during infection

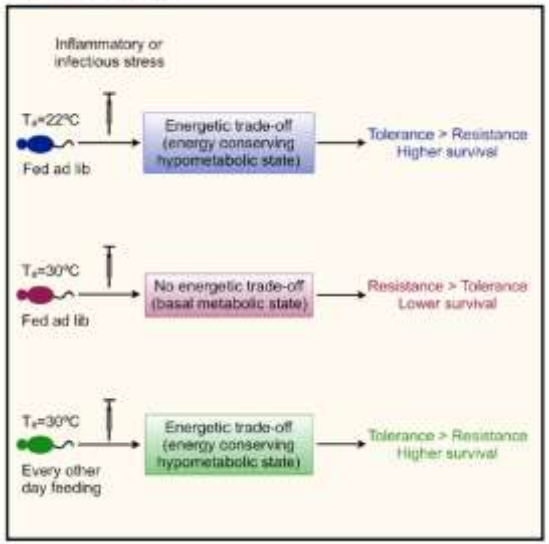
Prioritization is competitive:
- Inflammatory cytokines inhibit glucose consumption by liver, fat, and muscle.
- Muscles release substances that dampen immune responses



Cell

Energetic Trade-Offs and Hypometabolic States Promote Disease Tolerance

Graphical Abstract



Authors

Kirthana Ganeshan, Joni Nikkanen, Kevin Man, ..., D. Nyasha Chagwedera, James E. Cox, Ajay Chawla

Correspondence

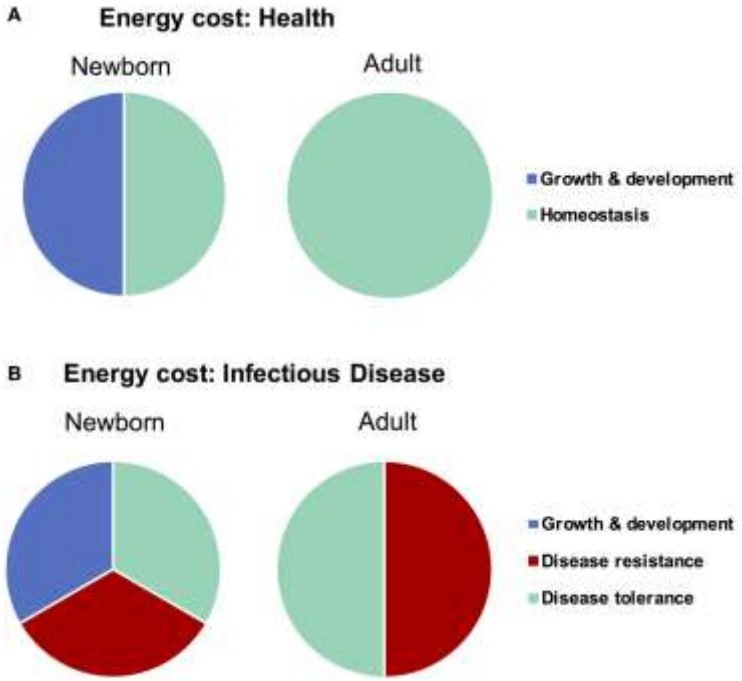
ajay.chawla@ucsf.edu

In Brief

Immune activation after infection is metabolically costly, competing for energy with the maintenance of normal body temperature, and this dynamic trade-off leads to preferential use of tolerance as a mechanism of bacterial defense.

Homeothermic regulation was independent of sickness behavior, was dependent on TLR4 signaling, and promoted disease tolerance to bacterial infections

Newborn energetic demands likely dictate immunity, and the demand hierarchy is mostly unknown



Harbeson D *et al. Front Immunol*