

Protection of newborn infants through vaccination

Tobias R. Kollmann MD PhD

Professor of Systems Biology and

Paediatric Infectious Diseases

Perth Children's Hospital

Telethon Kids Institute Perth, Australia



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Tobias R. Kollmann MDPHd
Professor of Systems Biology and
Paediatric Infectious Diseases
Telethon Kids Institute
Perth, Australia

Arnaud Marchant MDPHd
Director, Institute for
Medical Immunology
Université libre de Bruxelles,
Brussels, Belgium

Sing Sing Way MDPHd
Director Center for
Inflammation and Tolerance
Cincinnati Children's Hospital
Cincinnati, OH, USA



Protection of newborn infants through vaccination

Synopsis

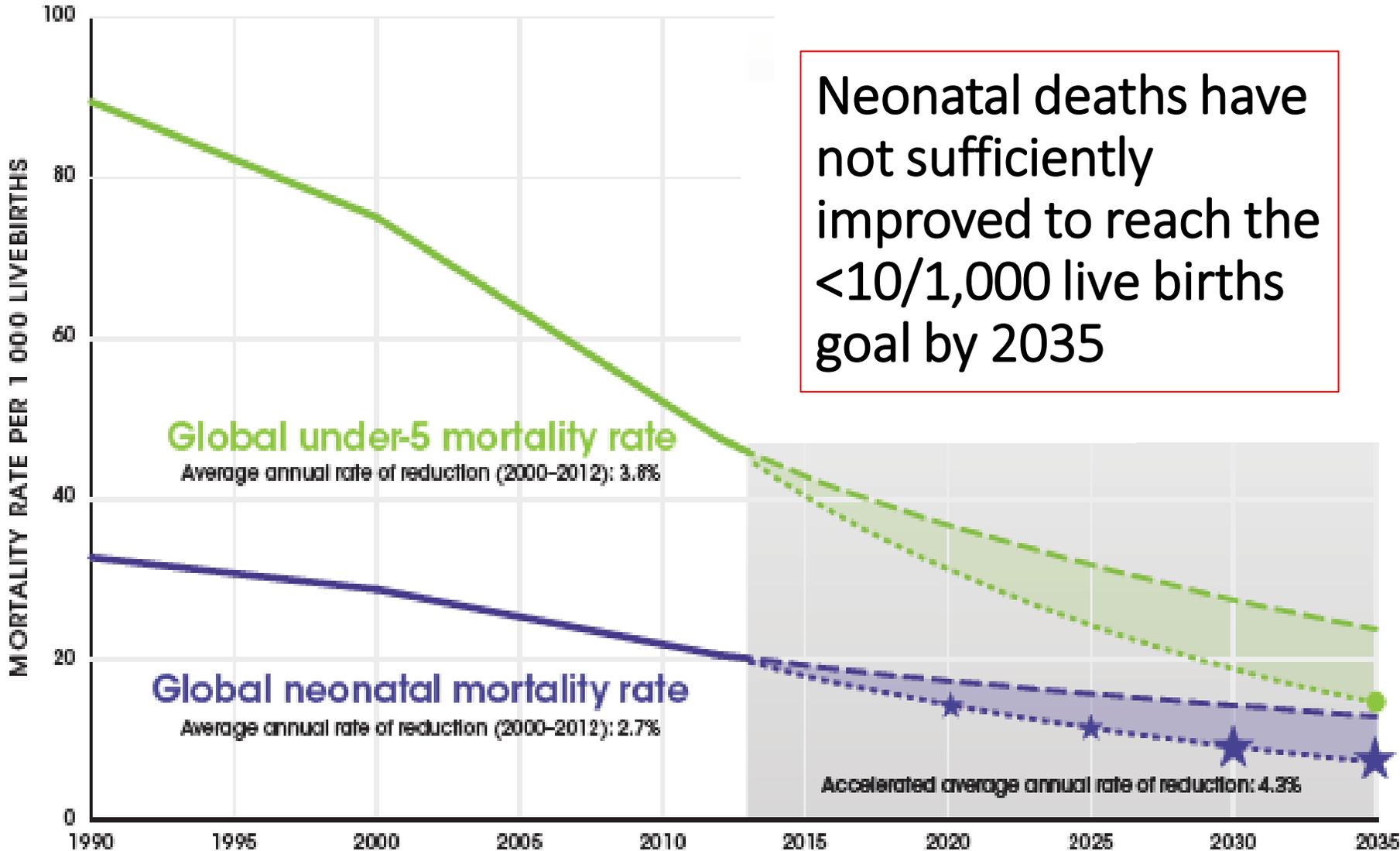
- 1. Immunizing the newborn to protect the newborn via pathogen-specific immunity has not worked.*
- 2. Immunizing the mother to protect the newborn via pathogen-specific immunity works, but will remain limited.*
- 3. Pathogen-agnostic effects of newborn immunization can protect the newborn.*
- 4. Pathogen-agnostic effects of immunizing the mother-newborn dyad may help protect the newborn.*

Protection of newborn infants through vaccination

I. What do we know?

II. How can we optimize vaccine-mediated protection for neonates?

What do we know?

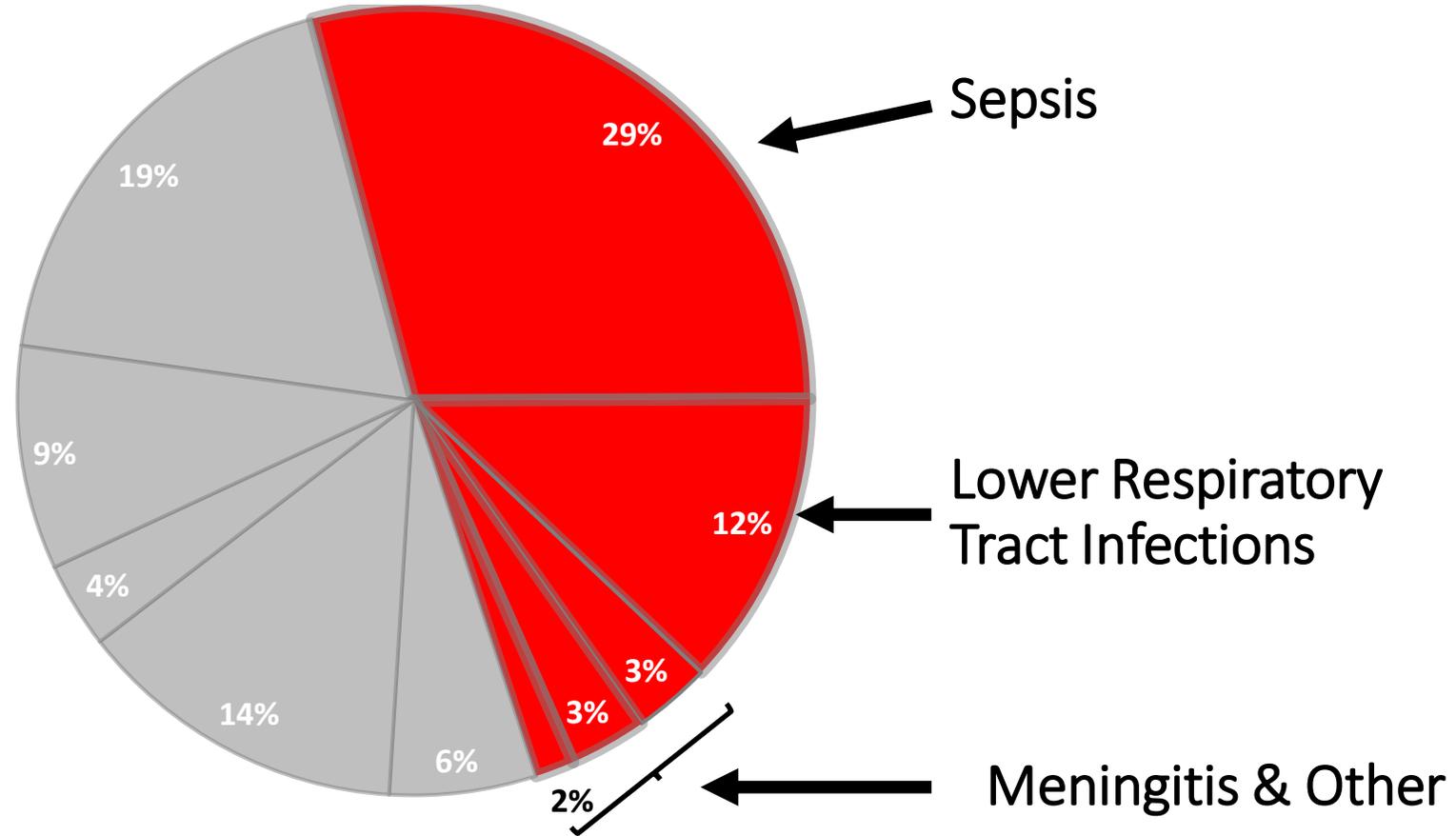


Source: *The Lancet* Every Newborn Series, Lawn JE et al. *Lancet*, 2014 (9).

What do we know?

Cause of death in neonates

Infectious disease causes ~ 50% of all neonatal deaths



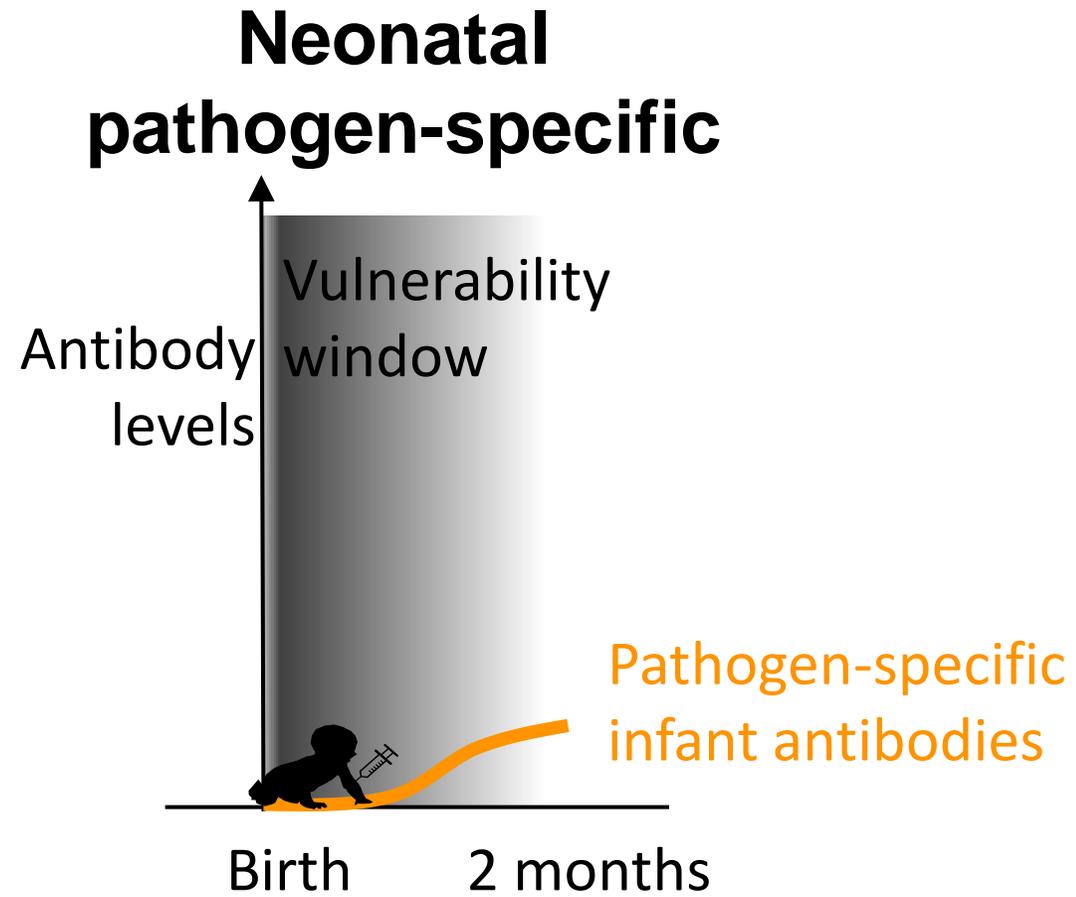
Preliminary data from CHAMPS; Courtesy of Shabir Madhi, University of Witwatersrand, South Africa

What do we know?

Timing of death in neonates



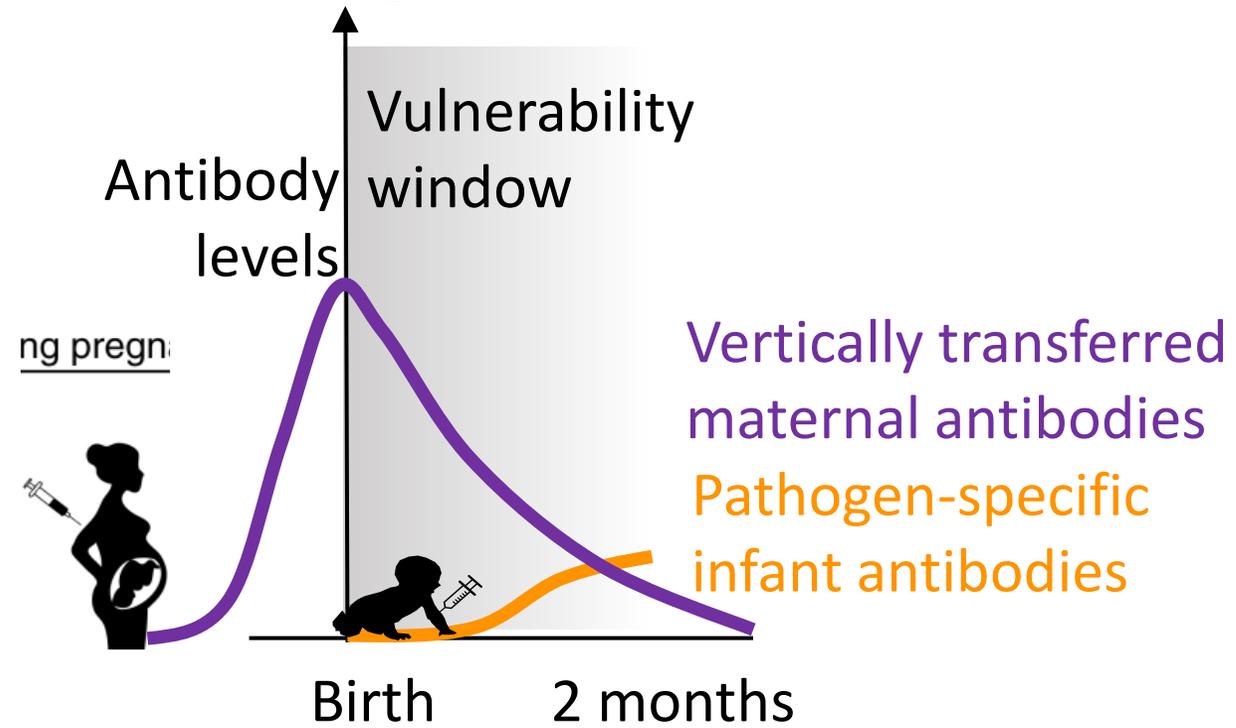
What do we know?



What do we know?

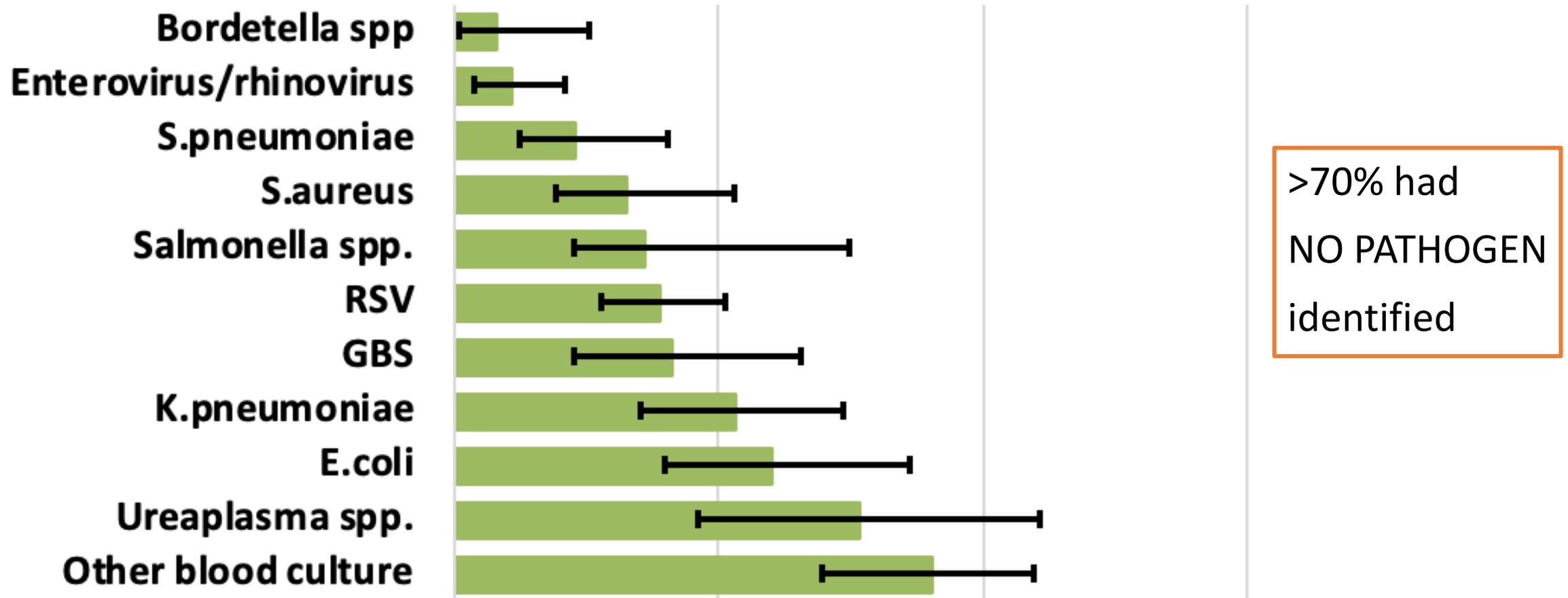
Neonatal / Maternal pathogen-specific

Tetanus
Influenza
Pertussis



What do we know?

Causes of severe 'infectious disease' in neonates



What do we know?

Current approach of vaccine-mediated, pathogen-specific protection of newborn not working

Reasons:

i) wrong timing

ii) wrong/incomplete targets

I. What do we know?

II. How can we optimize vaccine-mediated protection for neonates?

How can we optimize vaccination for neonates?

1. Throw out dogma
2. Strengthen maternal - newborn dyad as one biological unit

REVIEW

Vaccination strategies to enhance immunity in neonates

Tobias R. Kollmann^{1*†}, Arnaud Marchant^{2*†}, Sing Sing Way^{3†}

Science **368**, 612–615 (2020)



How can we optimize vaccination for neonates?

Pathogen-agnostic effects

A) Newborn Immunization

B) Immunization of the Maternal-Newborn Dyad

How can we optimize vaccination for neonates?

pathogen-agnostic effects



Vaccinology: time to change the paradigm?

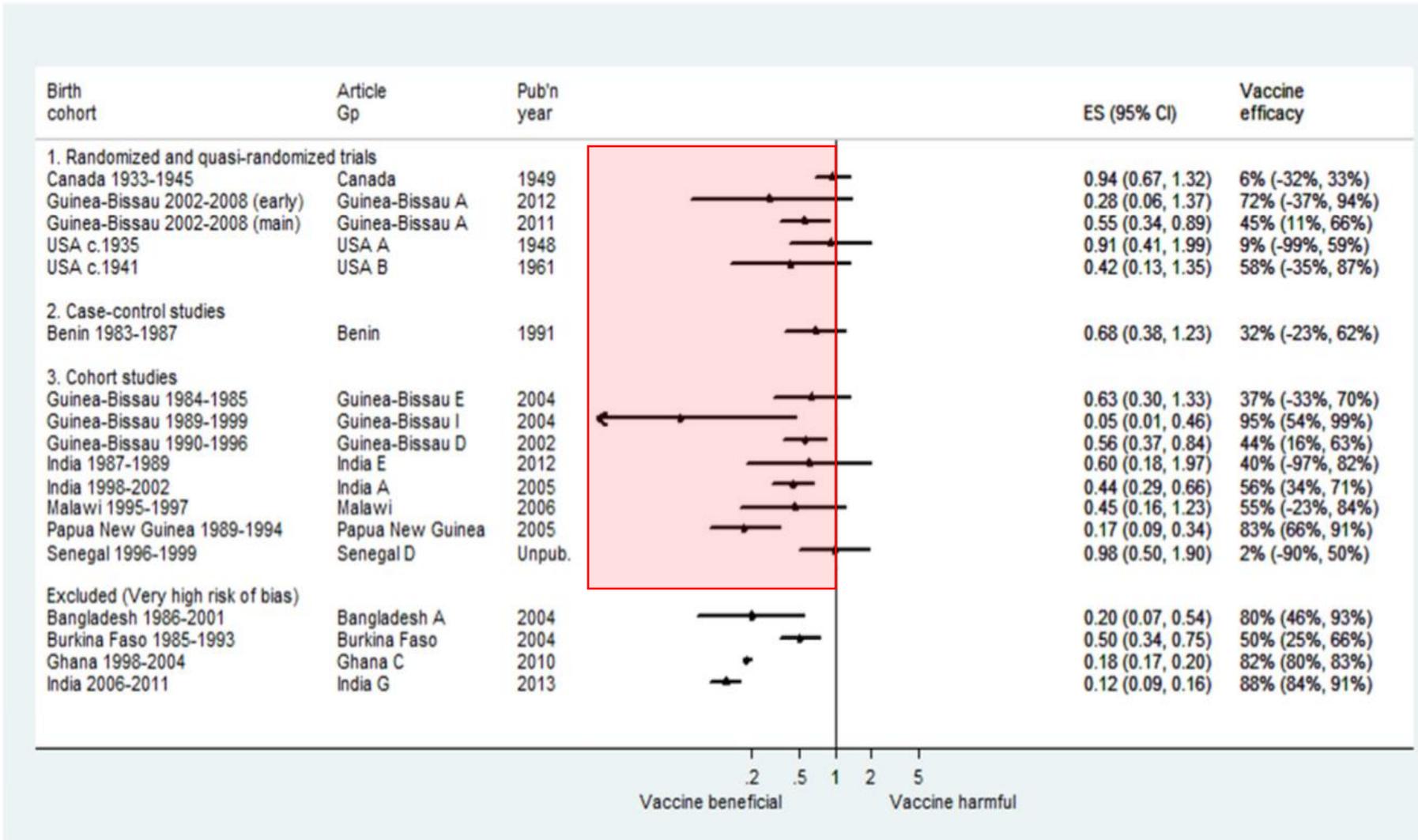
Christine Stabell Benn, Ane B Fisker, Andreas Rieckmann, Signe Sørup, Peter Aaby

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

THE LANCET
Infectious Diseases

How can we optimize vaccination for neonates?

Newborn immunization: pathogen-agnostic effects



WHO review concludes:

Neonatal BCG reduces mortality far beyond TB.

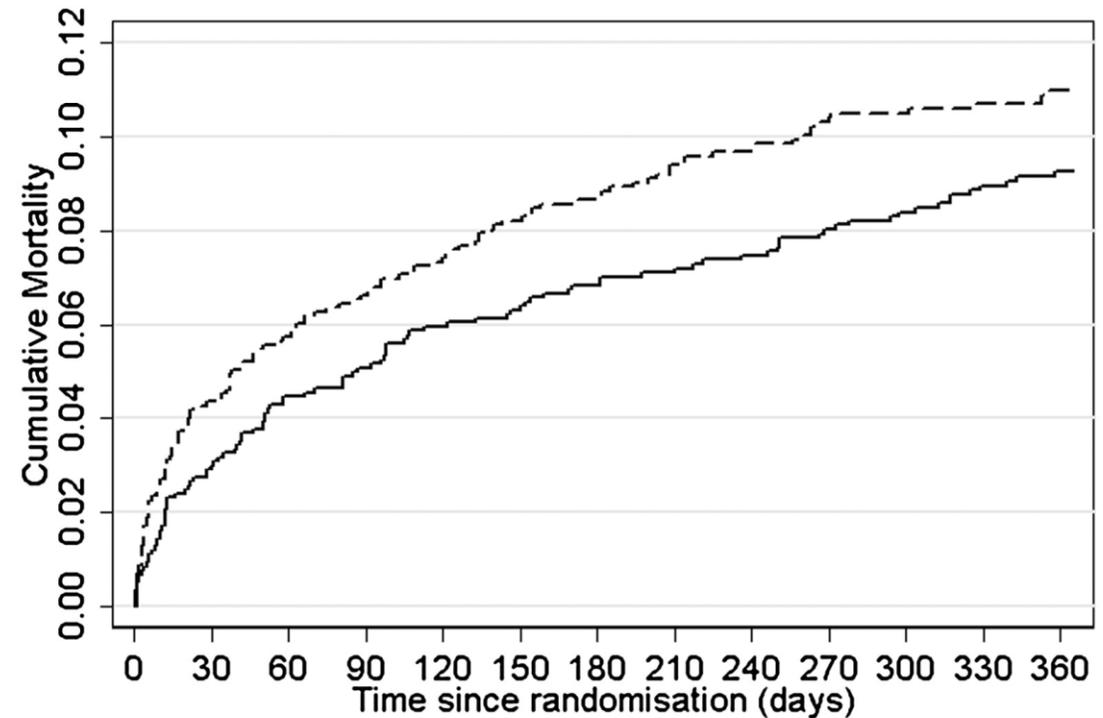
How can we optimize vaccination for neonates?

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 Lone Stensballe,³ Birgitte Rode Diness,¹ Karen Rokkedal Lausch,¹ Najaaraq Lund,¹ Sofie Biering Hilton Whittle,⁵ and Christine Stabell Benn^{1,3}

- At 1 month, mortality rate of BCG group 45% less than unvaccinated infants
- 53% lower for very low birth weight infants

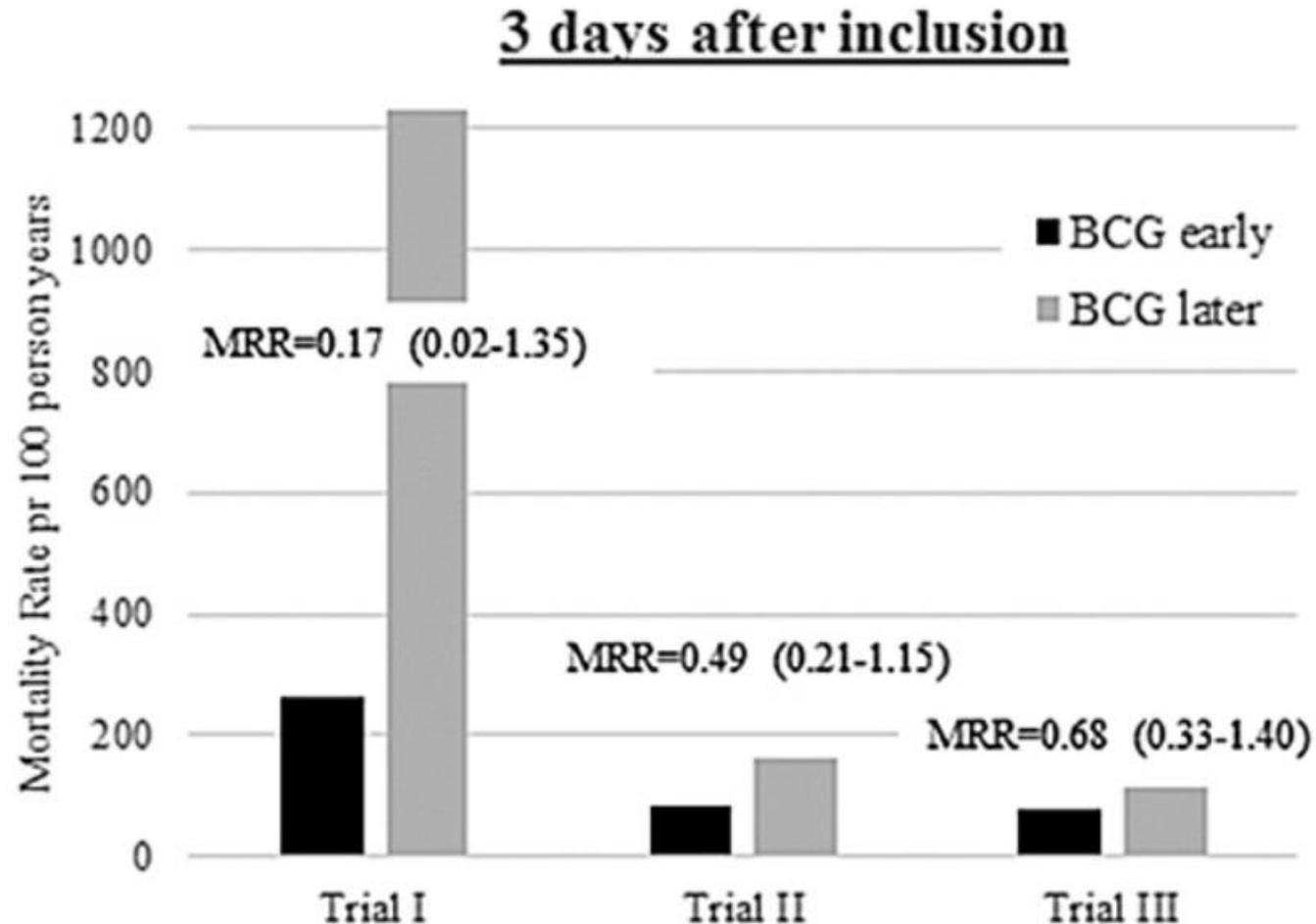


Number at risk	0	30	60	90	120	150	180	210	240	270	300	330	360
No BCG	1152	1079	1047	1023	972	954	723						
BCG	1168	1104	1073	1051	1004	992	732						

Randomised to: - - - - No BCG ——— BCG

How can we optimize vaccination for neonates?

Newborn immunization: pathogen-agnostic effects



BCG reduces MRR by ~ 50%
in the 3 days following
vaccination

Meta analysis: MRR=0.55 (0.32-0.93); p=0.027

How can we optimize vaccination for neonates?

Newborn immunization: pathogen-agnostic effects

1 FEBRUARY

Correspondence

PMID: 22147789

Non-specific effects of BCG?

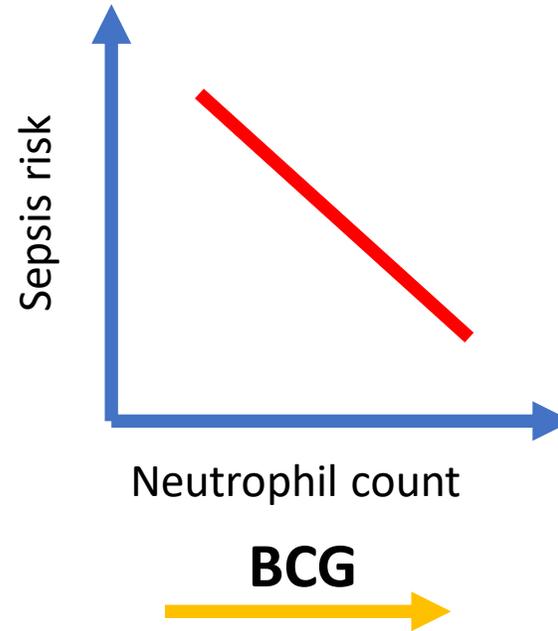
TO THE EDITOR—We would like to comment on the data presented by Aaby et al regarding their randomized trial of BCG in low-birth-weight children [1].

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.

How can we optimize vaccination for neonates?

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

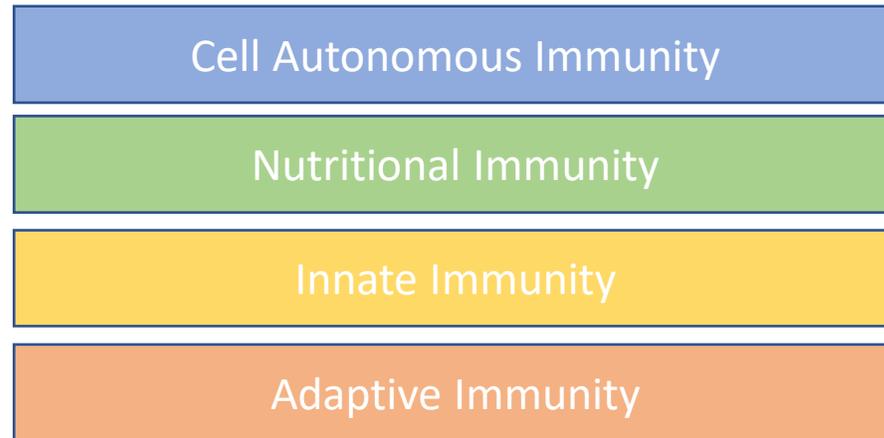
BCG vaccination–induced emergency granulopoiesis provides rapid protection from neonatal sepsis

Byron Brook¹, Danny J. Harbeson¹, Casey P. Shannon^{2,3}, Bing Cai⁴, Daniel He^{1,2,3}, Rym Ben-Othman⁴, Freddy Francis¹, Joe Huang⁴, Natallia Varankovich⁴, Aaron Liu¹, Winnie Bao⁴, Morten Bjerregaard-Andersen^{5,6,7}, Frederik Scholtz-Buchholzer^{5,6,8}, Lilica Sanca⁵, Christian N. Golding^{5,6}, Kristina Lindberg Larsen^{5,6}, Ofer Levy^{9,10,11}, Beate Kampmann^{12,13}, The EPIC Consortium*, Rusung Tan¹⁴, Adrian Charles¹⁴, James L. Wynn¹⁵, Frank Shann¹⁶, Peter Aaby⁵, Christine S. Benn^{5,6,8}, Scott J. Tebbutt^{2,3,17}, Tobias R. Kollmann^{1,4,18†‡}, Nelly Amenyogbe^{1,18†‡}

How can we optimize vaccination for neonates?

Newborn immunization: pathogen-agnostic effects

BCG can impact all 'layers' of host immunity!



- **Autophagy (bladder cancer therapy)**
- **Rapid drop in free serum iron**
- **Hematopoiesis & Trained Immunity**
- **Increases response of other vaccines**

Immunity 2017 Mar 21;46(3):350-363

PLoS Pathog 10(10): e1004485

Journal of bacteriology. 1969;100(1):64-70

SciTranslMed 12:, May 2020

Seminars in Immunology 26 (2014) 512–517

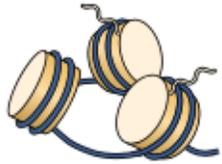
J. Imm 2002; 168:925

Vaccine 2019; 37:3735

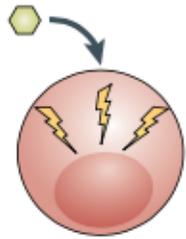
How can we optimize vaccination for neonates?

Newborn immunization: pathogen-agnostic effects

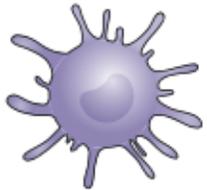
HOW?



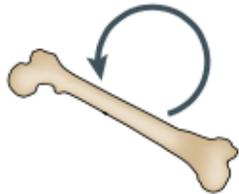
Epigenetic modifications



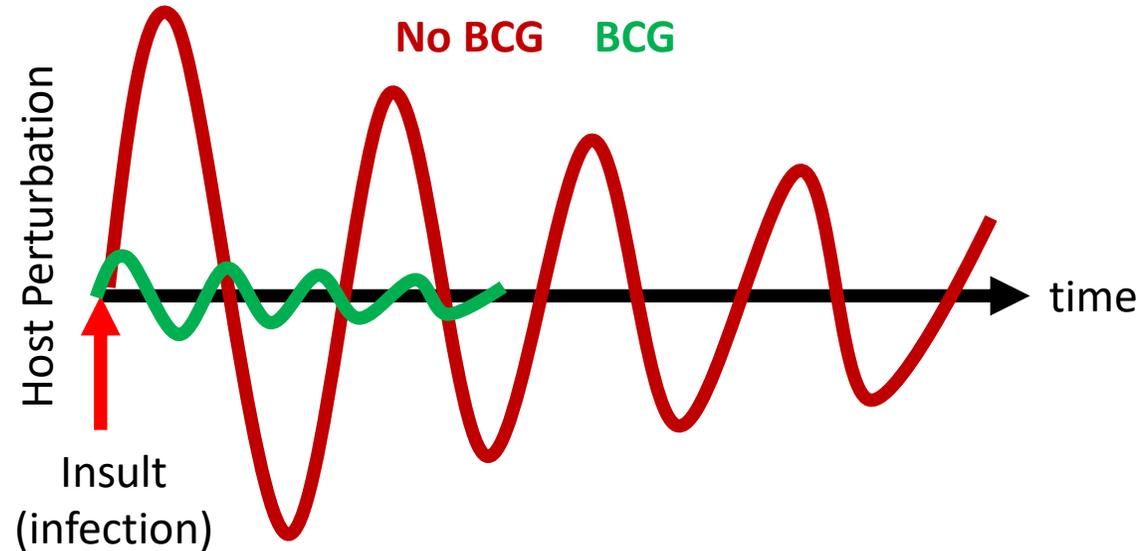
Metabolic reprogramming



↑ Altered responsiveness

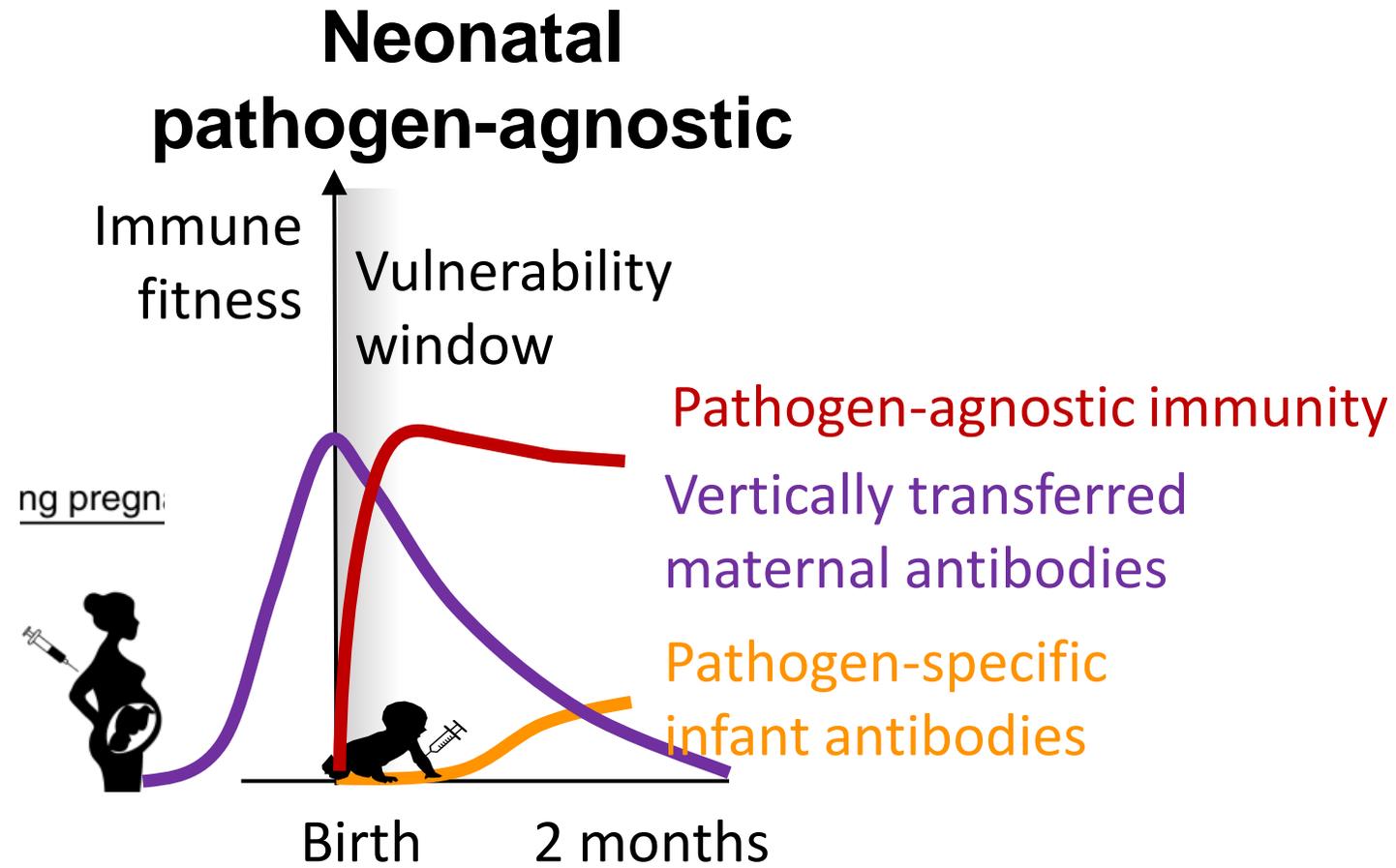


Long-term effects



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

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How can we optimize vaccination for neonates?

Pathogen-agnostic effects

A) Newborn Immunization

B) Immunization of the Maternal-Newborn Dyad

How can we optimize vaccination for neonates?

Immunization of Maternal-Newborn Dyad: pathogen-agnostic enhancement?

Maternal Priming: Bacillus Calmette-Guérin (BCG)
Vaccine Scarring in Mothers Enhances the Survival of
Their Child With a BCG Vaccine Scar

Journal of the Pediatric Infectious Diseases Society 2020;9(2):166–72



SCIENTIFIC REPORTS | 7: 17366

- Infant BCG scar was associated with a 41% lower mortality (confirming previous trials)
- Mortality reduction was 66% if infant & mother had BCG scar but only 8% if the mother had no BCG scar

~ Vertical Prime-Boost of Maternal-Newborn Dyad

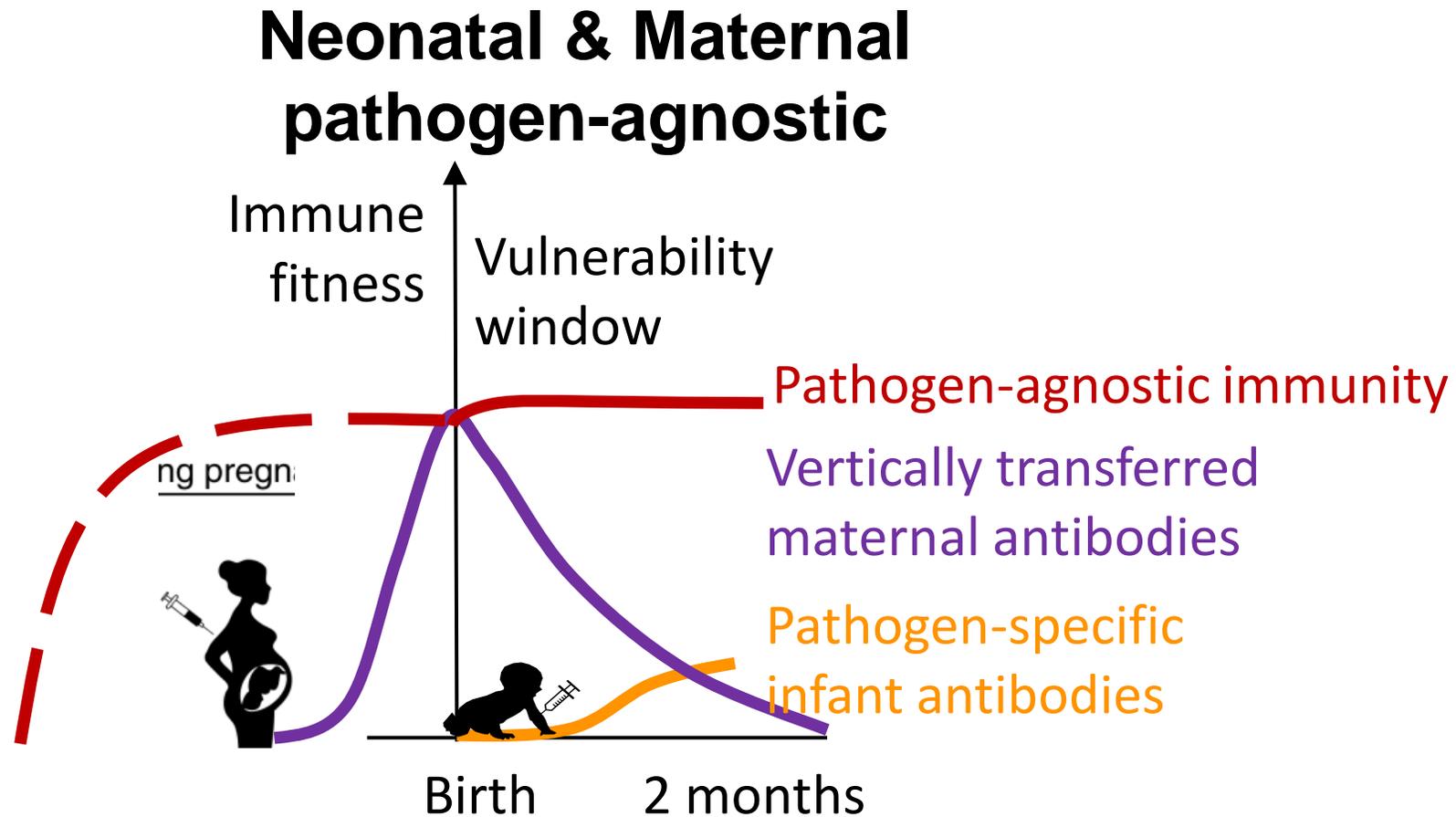
How?

Maybe maternal antibody?

Maybe BCG itself?

...

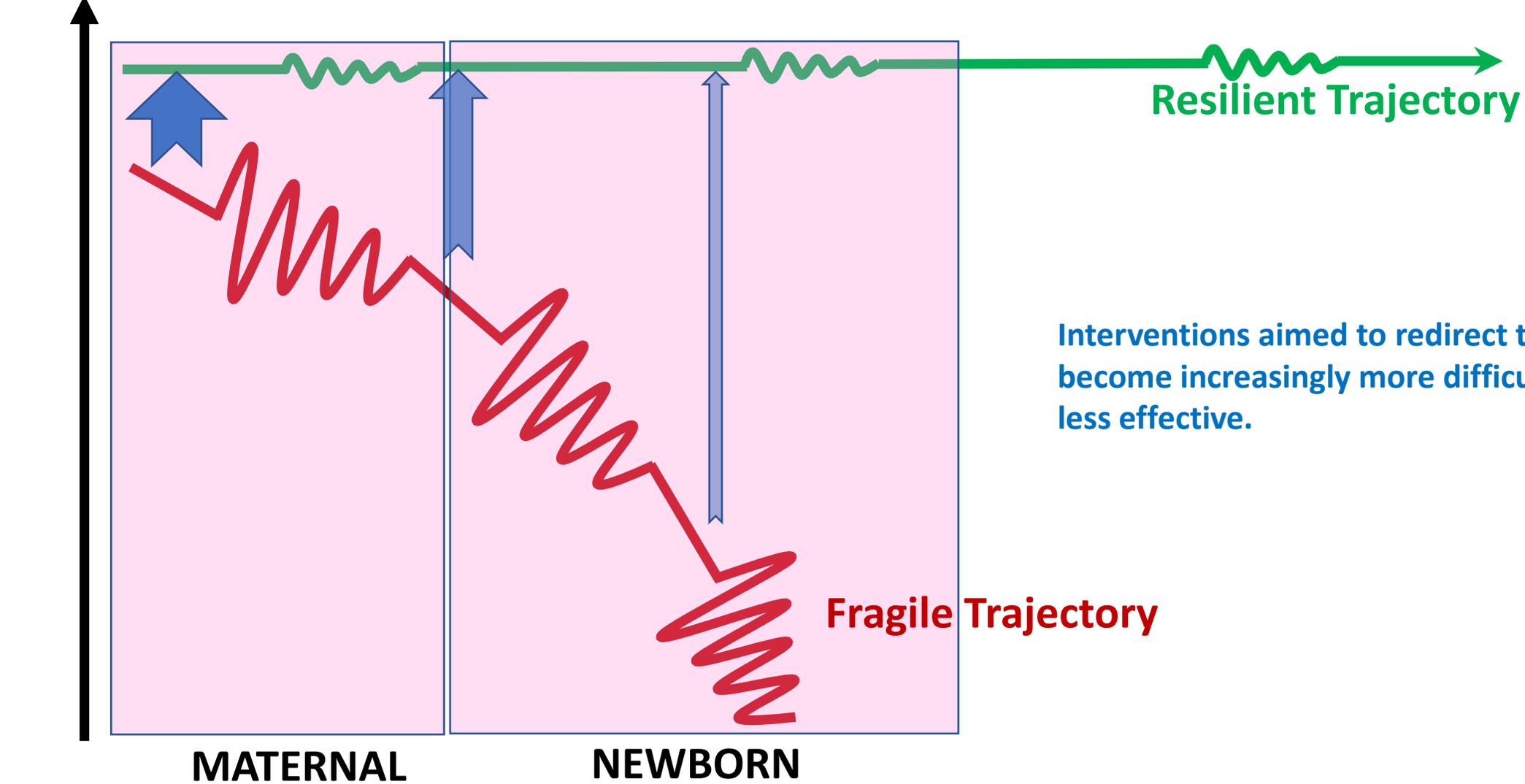
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Maternal-Newborn Dyad: One trajectory

Maternal-Newborn Dyad: One trajectory

HEALTH



How can we optimize vaccination for neonates?

Conclusions to optimize vaccine-mediated protection for newborns:

- 1. Immunizing the newborn to protect the newborn has not, does not, and will not work via pathogen-specific, adaptive immunity.*
- 2. Pathogen-specific protection via maternal immunization works well, but the range of pathogens we would need to target limits global impact.*
- 3. Pathogen-agnostic effects of newborn immunization (BCG) can provide broad & immediate protection to neonates.*
- 4. Immunization of the mother-newborn dyad may further enhance pathogen-agnostic protection of the neonate.*

Thank You

tkollm@mac.com

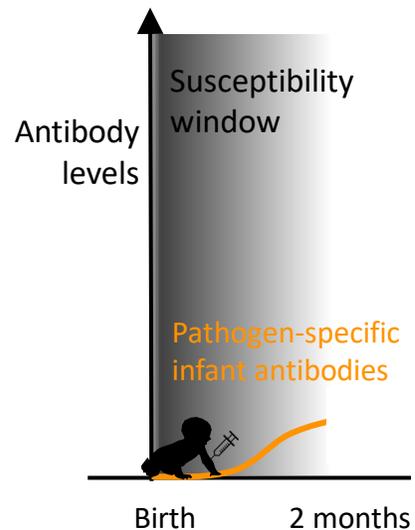
SingSing.Way@cchmc.org

Arnaud.Marchant@ulb.be

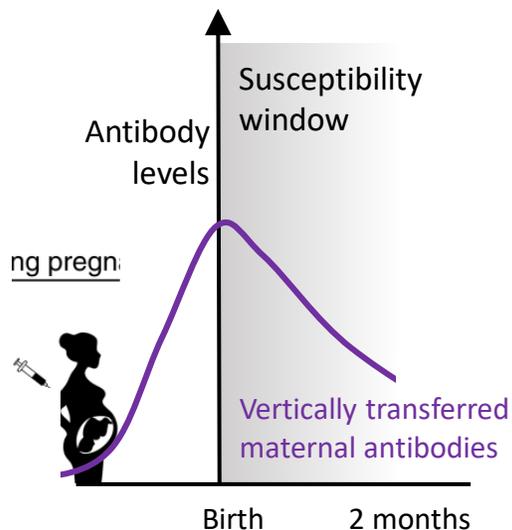
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(graphical summary)

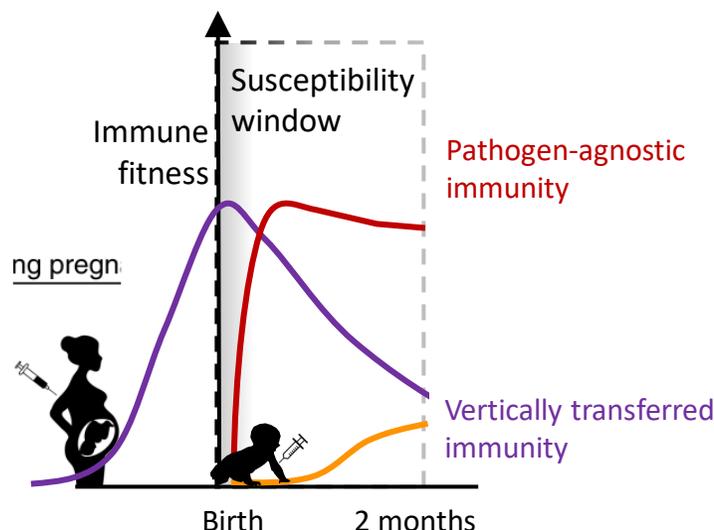
A. Neonatal pathogen-specific



B. Maternal pathogen-specific



C. Neonatal pathogen-agnostic



D. Maternal & Neonatal pathogen-agnostic

