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

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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

Newborn deaths/1,000 live births
PART II: The main problem (existing dogma)

When & what do newborns die of?

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth complications</td>
<td>35%</td>
</tr>
<tr>
<td>Intrapartum-related complications</td>
<td>24%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>15%</td>
</tr>
<tr>
<td>Congenital abnormalities</td>
<td>11%</td>
</tr>
<tr>
<td>Other</td>
<td>7%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>1%</td>
</tr>
<tr>
<td>Tetanus</td>
<td>1%</td>
</tr>
</tbody>
</table>


PART II: The main problem (existing dogma)
When & what do newborns die of?

- Preterm birth is a DIRECT cause of 35% of all neonatal deaths
- Preterm birth complications: 1.08 million
- Neonatal infections: 0.83 million

INDIRECT
Moderate and late preterm birth increase the chance of dying from infections

Preterm birth is a risk factor for neonatal and postneonatal deaths.
At least 50% of all neonatal deaths are preterm.
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BOOSTING BABY'S IMMUNITY

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PART II: The main problem (existing dogma)
When & what do newborns die of?


PART II: The main problem (existing dogma)

Timing of death in neonates

Vulnerability window

Birth  2 months
PART II: The main problem (existing dogma)

Vulnerability window

Antibody levels

Pathogen-specific infant antibodies

Birth  2 months
PART II: The main problem (existing dogma)

Pathogen-specific infant antibodies

Vertically transferred maternal antibodies

Tetanus
Influenza
Pertussis
SARS-CoV-2

Birthday 2 months

Antibody levels

Vulnerability window
PART II: The main problem (existing dogma)

Causes of severe ‘infectious disease’ in neonates

- Bordetella spp
- Enterovirus/rhinovirus
- S.pneumoniae
- S.aureus
- Salmonella spp.
- RSV
- GBS
- K.pneumoniae
- E.coli
- Ureaplasma spp.
- Other blood culture

>70% had NO PATHOGEN identified
PART II: The main problem (existing dogma)

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

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

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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)
Acknowledgements: it takes a village

Nelly Amenyogbe  Byron Brook  Peter Aaby  Christine Stabell Benn
PART III: The solution (existing vaccines)

“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.

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?

- 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
PART III: The solution (existing vaccines)

Newborn immunization: pathogen-agnostic effects

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.
Subcutaneous BCG vs no vaccination

Sepsis Challenge (IP injection of cecal slurry)

Day of life (DOL) 4

DOL 7

Recovery over time (0-96hr)

Bacterial burden 24hr after challenge
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 Granulopoiesis: 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.
The underlying mechanism: current understanding

I. Septic death in newborn mice

II. Septic survival post BCG vaccination
Newborn immunization: pathogen-agnostic effects

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

Vertically transferred maternal antibodies
Pathogen-specific infant antibodies

Antibody levels
Vulnerability window

Birth 2 months
PART III: The solution (existing vaccines)

- Pathogen-agnostic immunity
- Vertically transferred maternal antibodies
- Pathogen-specific infant antibodies
PART IV: The *main* solution (switch focus to host)

- **Immune Resilience**
  - Vulnerability window
  - Pathogen-agnostic immunity
  - Vertically transferred maternal antibodies
  - Pathogen-specific infant antibodies

Birth 2 months
PART IV: The main solution (switch focus to host)

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

HOW?

Epigenetic modifications
Metabolic reprogramming

↑ Altered responsiveness
Long-term effects

Host Perturbation
Insult (infection)

time

No BCG
BCG

Nature Reviews Immunology 20, 375–388 (2020)
PART IV: The *main* solution (switch focus to host)

**HOW?**

- Epigenetic modifications
- Metabolic reprogramming
- Altered responsiveness
- Long-term effects

![Graph showing the relationship between time, host perturbation, and infection](image)

- No BCG
- BCG

*Host Perturbation*

- Insult (infection)

*Time*

*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 (incl. of existing vaccines)
- The **main solution** is to switch our focus from pathogen to the host
Thank You

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Resilience/Fitness is dictated by host metabolism

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
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