

Enhancing early life immunity – a global perspective

'Saving Newborn Lives Through a Paradigm Shift'

Tobias R. Kollmann MD PhD

Division of Infectious Disease; Department of Pediatrics

University of British Columbia, Vancouver, Canada



Disclosure Statement

I have no affiliation (financial or otherwise) with a pharmaceutical, medical device or communications organization.

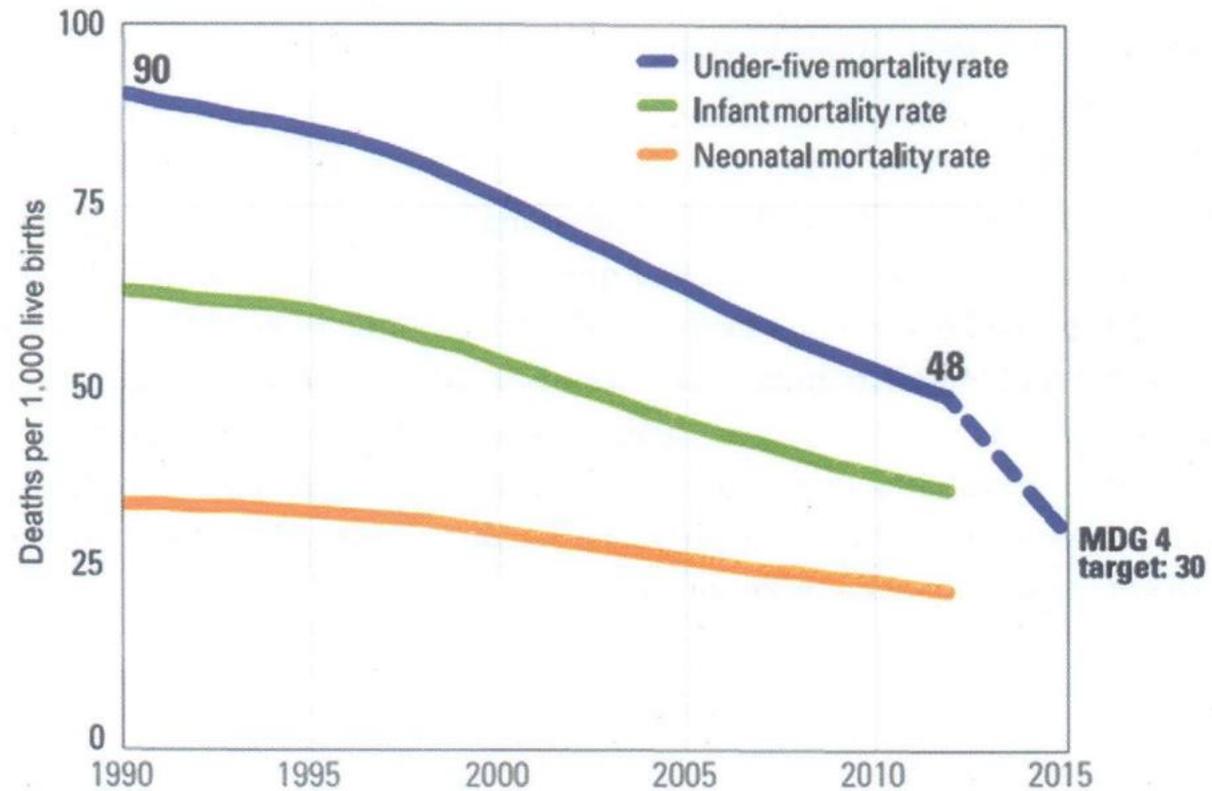
Learning Objectives

- Appreciate why enhancing early life immunity is important
- Provide overview of what options exist to enhance early life immunity
- Recognize the current gaps
- Appreciate what the research community can and must contribute to increase knowledge of enhancing early life immunity

'Paradigm Shift' to save newborn lives

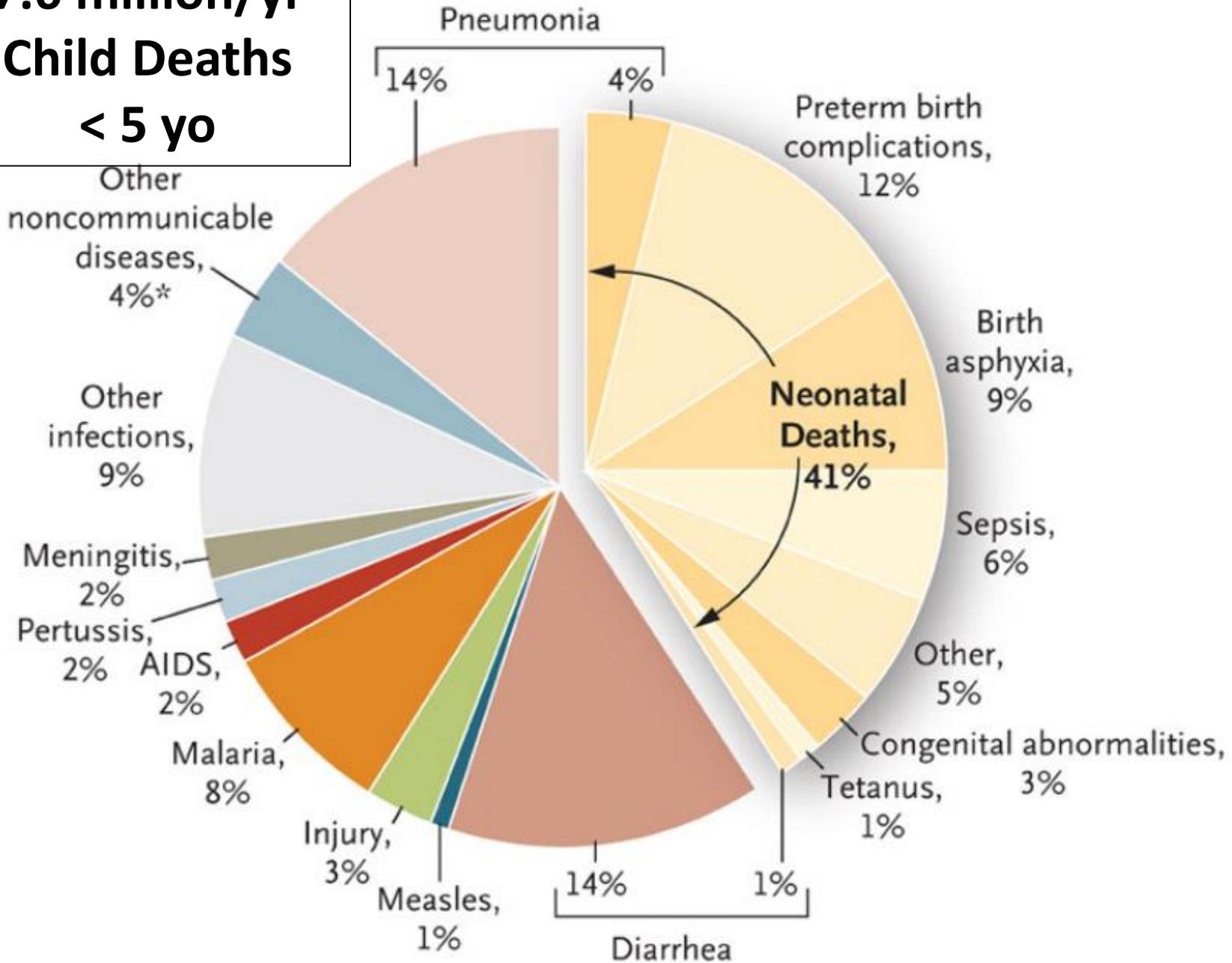
- Neonatal infectious mortality remains high, especially in resource limited settings
- **Interventions that focus on strengthening the neonatal host rather than protecting from few specific pathogens would prevent many infectious threats at the same time.**
- These host-focused interventions are cheap and easy to implement locally, and are available now.

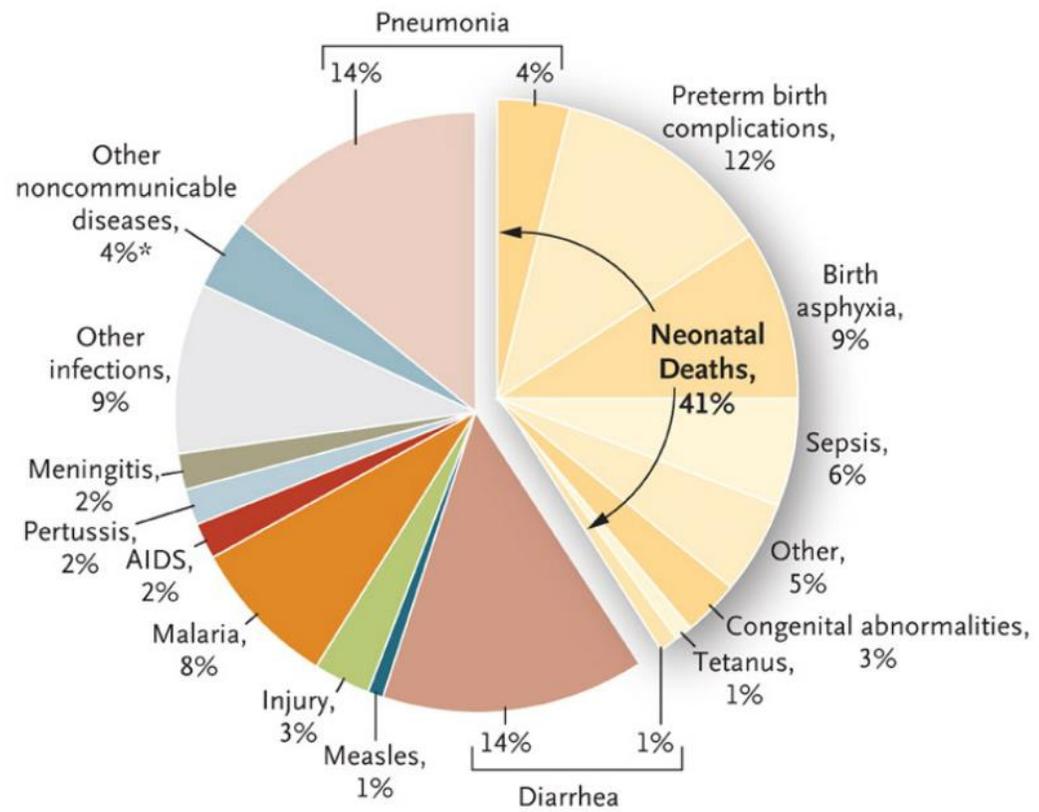
What is the problem?

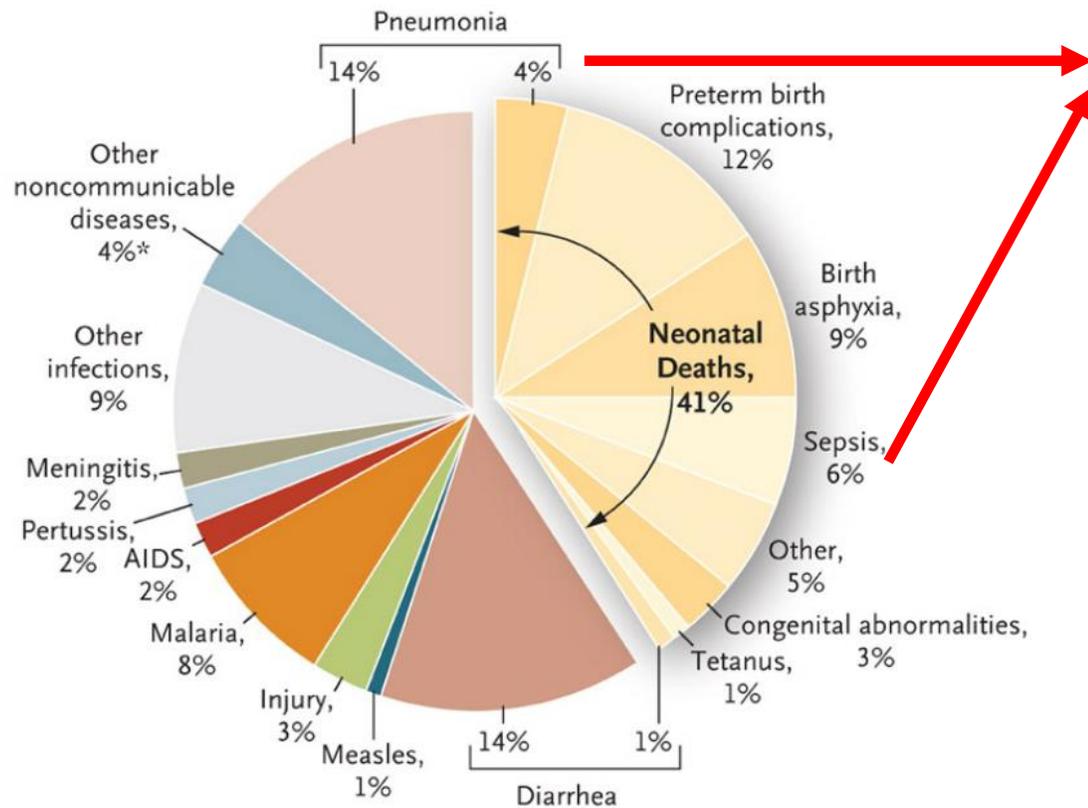


Source: UNICEF 2013. 2013 Statistical snapshot: Child Mortality¹⁰.

7.6 million/yr Child Deaths < 5 yo







Most common neonatal pathogens across the world:

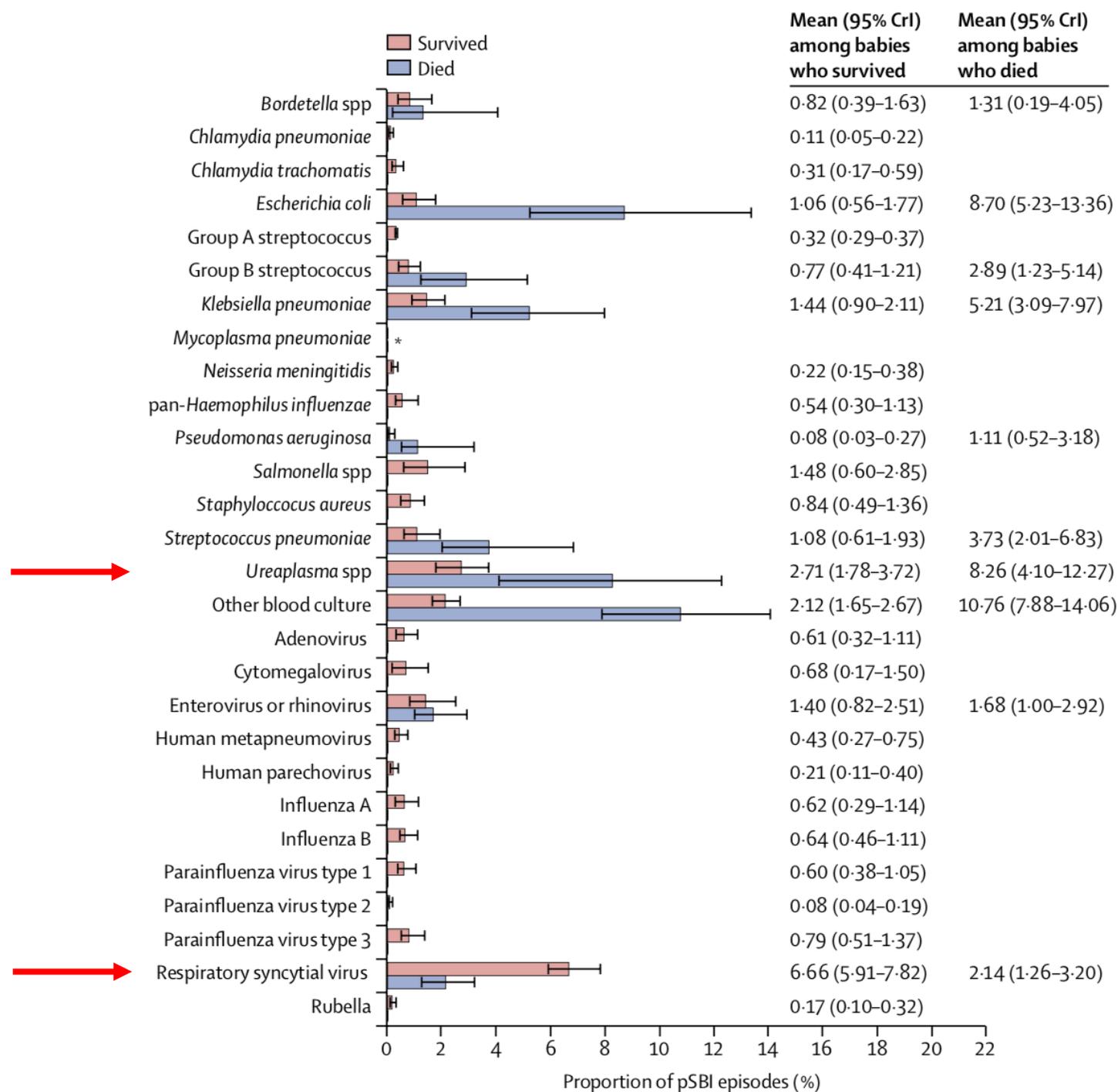
- Escherichia coli
- Staphylococcus aureus
- Klebsiella pneumoniae
- Streptococcus pneumoniae
- Pseudomonas
- *Acinetobacter* spp

Antibiotic resistance ~ 44%
(and increasing)

Hamer *Pediatr Infect Dis J* 2015;34:e1–e8

We do not have much to offer to prevent the globally most prevalent newborn infections ☹

Causes and incidence of community-acquired serious infections among young children in south Asia (ANISA): an observational cohort study



Pathogen to Host Paradigm Shift: Summary

1. Many neonatal deaths are due to infections (for which we currently have no effective way to protect newborns from).

Host-focused Interventions:

1. reduce exposure

and/or

2. increase defense

- 1. Reduce exposure
 - **Cleaner birth**
 - Chlorhexidine umbilical cord cleansing at and after delivery reduces exposure to pathogens and neonatal infection (Arifeen *Lancet* 2012; **379**(9820): 1022-8)
 - **Clean water**
 - the provision of clean drinking water and reliable sanitation, including the water, sanitation and hygiene (WASH) campaigns was promising (Velleman *PLoS medicine* 2014; **11**(12): e1001771), but did NOT work (*Lancet Glob Health*. 2018 Mar;6(3):e316-e329; *Lancet Glob Health*. 2018 Mar;6(3):e302-e315)
 - **Reducing crowding** can decrease transmission of respiratory and intestinal infections (Colosia *BMC infectious diseases* 2012; **12**: 95)
 - However, this obstacle is largely linked to poverty, a powerful factor that is difficult to redress on a large scale (Costello *BMJ* 2004; **329**(7475): 1166-8)

- 2. Increase host defense

- **Exclusive Breastfeeding**

- could prevent over 800,000 deaths (13 per cent of all deaths) in children under five years of age;
 - a breastfed child is 14 times less likely to die in the first six months of life than a non-breastfed child (*Black Lancet* 2013; **382**(9890): 372-5)

- **Nutrition**

- mortality in children younger than 5 years could be reduced by 15%, if populations could access evidence-based nutrition interventions at 90% coverage (*Bhutta Lancet* 2013; **382**(9890): 452-77)
 - However, not always:
 - supplemental iron given to iron-replete infants increases the risk for morbidity due to sepsis, malaria and non-typable *Salmonella spp.* infection (*Oppenheimer The Journal of nutrition* 2001; **131**(2s-2): 616S-33S)
 - VitA supplementation does not reduce mortality (e.g. trial in Ghana)(*Edmond Lancet* 2015 Apr 4;**385**(9975):1315-23)

- 2. Increase host defense
 - **Maternal vaccination targeting specific pathogens**
(see also Dr. Sadarangani's following talk)
 - maternal immunization against tetanus has globally decreased the rates of neonatal **tetanus** from 200,000 in the year 2000 to 49,000 in 2013
(Khan *International journal of women's health* 2015; **7**: 171-80)
 - protection of the newborn and young infant has also been documented following maternal immunization for **pertussis** and **influenza** (Amirthalingam *Lancet* 2014; **384**(9953): 1521-8; Madhi *N Engl J Med* 2014; **371**(10): 918-31)
 - currently considered to be added: Group B streptococcus (**GBS**) and Respiratory Syncytial Virus (**RSV**).
 - the relevance of these pathogens for low-resource settings is not always clear.

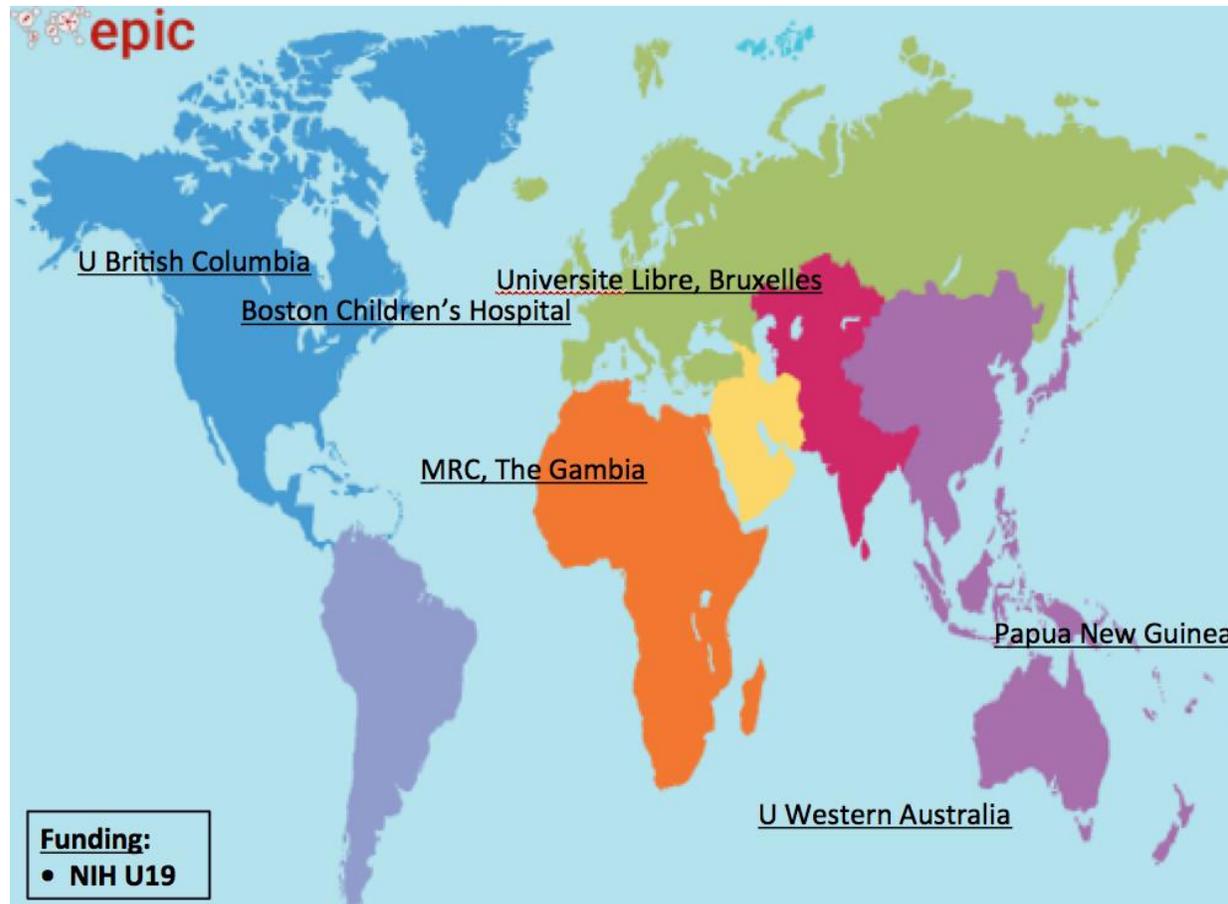
- 2. Increase host defense

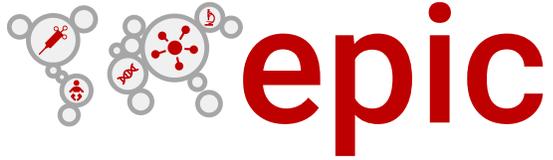
- **Vaccination of newborns targeting specific pathogens**

- Vaccines against poliomyelitis, hepatitis, tuberculosis, tetanus, diphtheria and measles are now given to >100 million children annually, preventing ~ 2.5 million deaths each year worldwide (Clemens *Nat Immunol* 2010; **11**(12): 1069-72)
 - Beyond reducing death and suffering, childhood vaccination also provide major economic benefits through medical cost savings (Barnighausen *Proc Natl Acad Sci U S A* 2014; **111**(34): 12313-9)
 - However, currently no (!) vaccines are given that address neonatal infectious pathogens, because
 - Vaccines don't exist for the relevant pathogens (Hamer *Pediatr Infect Dis J* 2015;34:e1–e8; ANISA Study, *Lancet* 392:145-59, 2018)
 - Neonatal vaccination is believed to not work well at inducing protective adaptive immune response (but maybe more dogma than fact)
 - **This leaves the newborn largely unprotected!**

- 2. Increase host defense
 - **Increase (improve) newborn vaccination**
 - How does the newborn respond to a successful vaccine (e.g. Hepatitis B, BCG (OPV))?

Expanded Program of Immunization Consortium





Specific Aims of EPIC HIPC

SPECIFIC AIM 1: Characterize the impact of pre-vaccine OMIC and immune *in vivo* signatures that predict immunogenicity of HBV in human newborns



***In vivo* manipulation
(association)**

SPECIFIC AIM 2: Interrogate functional correlations between OMICs and immune signatures on neonatal immune responses that predict immunogenicity of HBV in human newborns

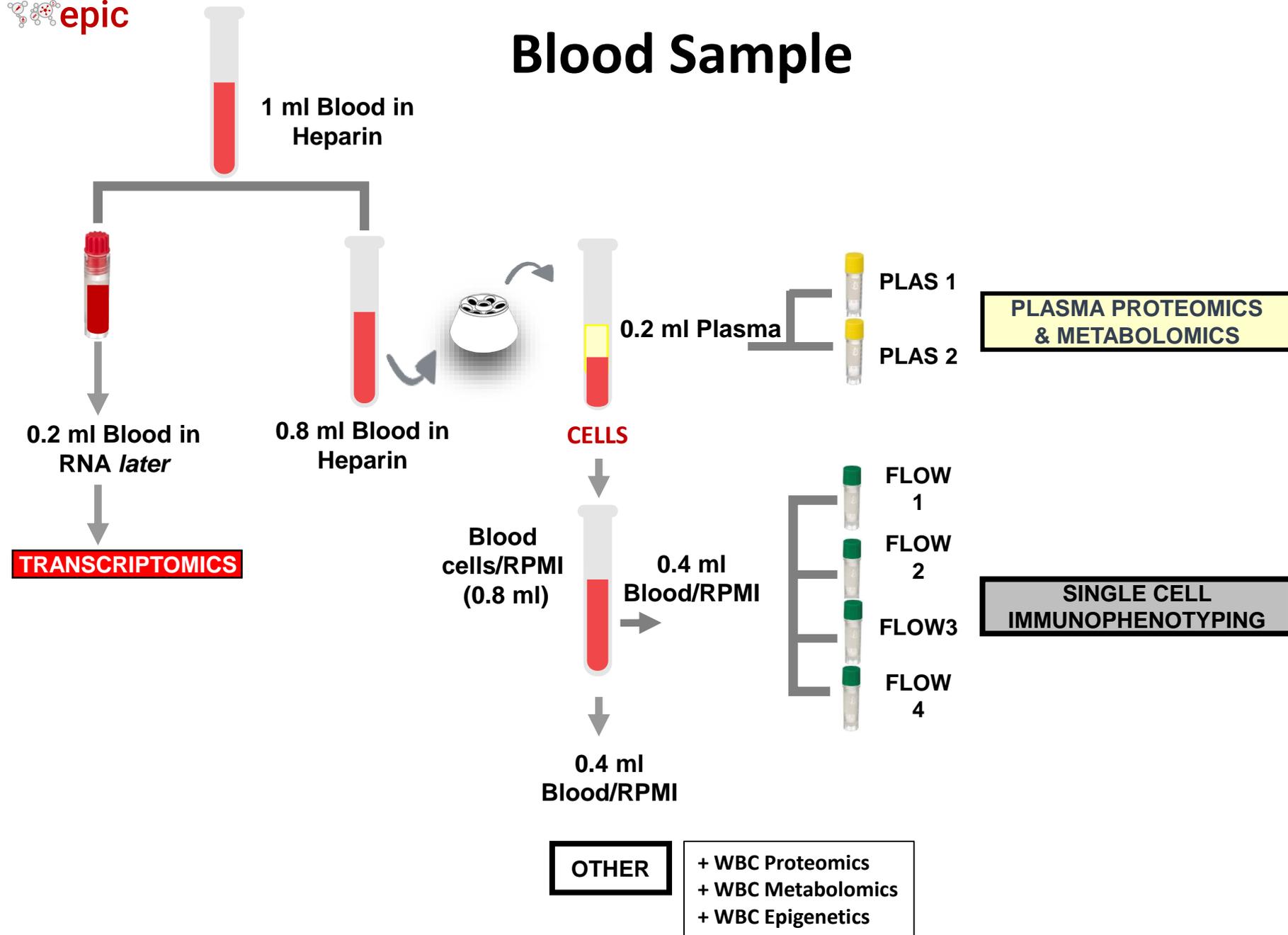


SPECIFIC AIM 3: Interrogate functional correlations between OMICs and immune signatures that predict immunogenicity of HBV in human newborns



***In vitro* manipulation
(cause & effect)**

Blood Sample





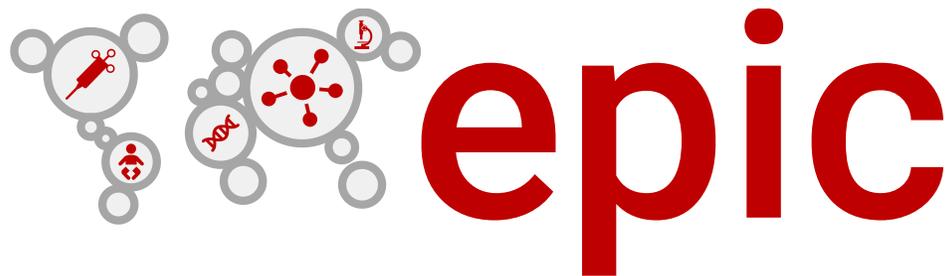
Dynamic molecular changes during the first week of human life follow a robust developmental trajectory

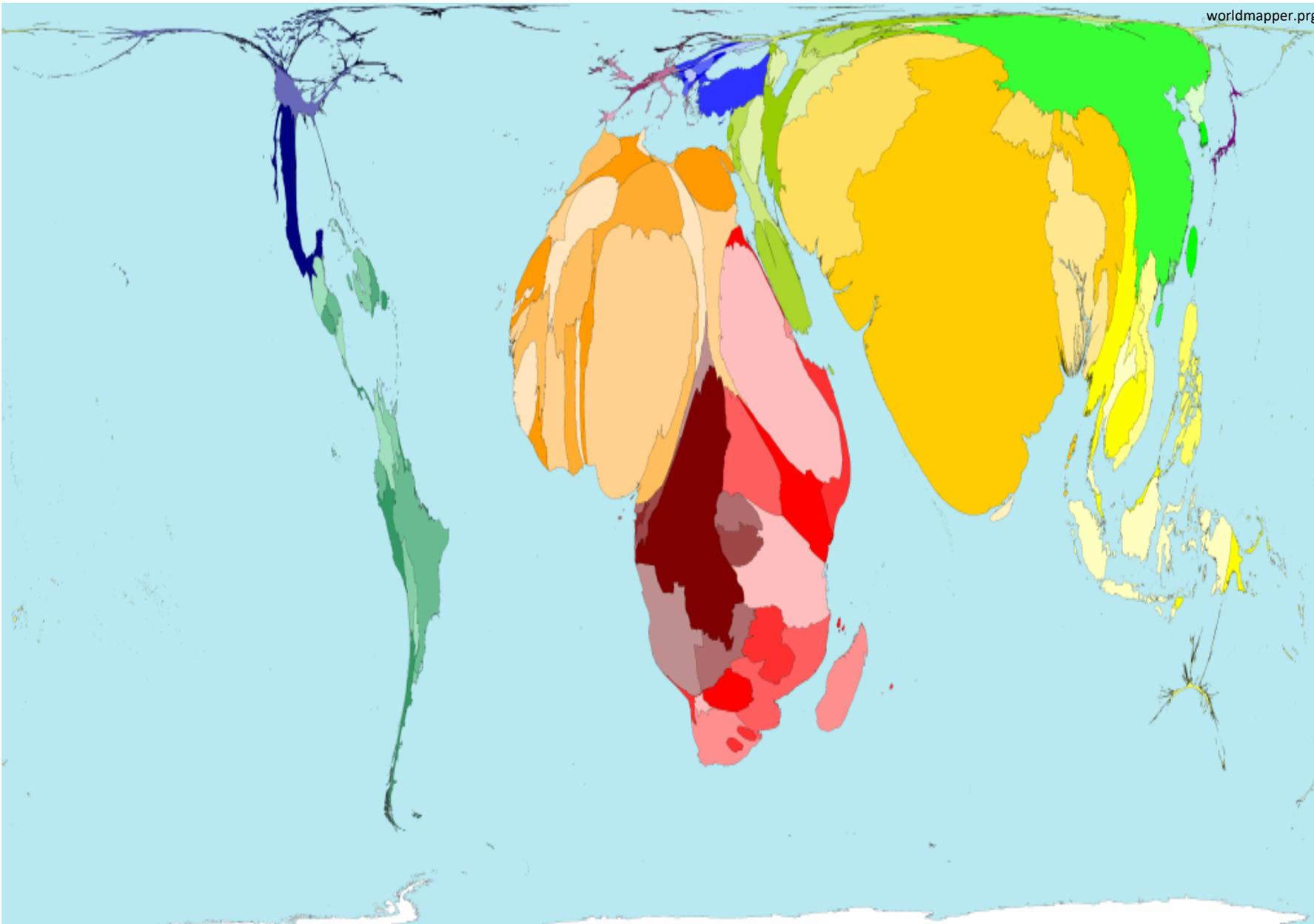
**Erin E. Gill^{1*}, Casey Shannon^{2*}, Nelly Amenyogbe^{1*}, Rym Ben-Othman^{3*},
Tue B. Bennike^{4,5,6,7*}, Joann Diray-Arce^{6,7*}, Olubukola Idoko^{8*}, Amy H.
Lee^{1*}, Simon van Haren^{6,7*}, Kim-Anh Lê Cao⁹, Momoudou Cox⁸, Alansana
Darboe⁸, Reza Falsafi¹, Davide Ferrari⁹, Daniel Harbeson¹⁰, Daniel He²,
Samuel H. Hinshaw¹¹, Jorjoh Ndure⁸, Jainaba Njie-Jobe⁸, Matthew A.
Pettengill^{6,7,12}, William S. Pomat¹³, Peter C. Richmond¹⁴, Elishia Roberts⁸,
Guzman Sanchez-Schmitz^{6,7}, Amrit Singh^{2,15}, Kinga K. Smolen^{6,7}, Anita H.J.
van den Biggelaar¹⁶, the EPIC Consortium¹⁷, #Ryan Brinkman^{18,19}, #Al
Ozonoff^{6,7,20}, #Hanno Steen^{5,6,7}, #Robert E.W. Hancock¹, #Scott J.
Tebbutt^{2,21,22}, #Beate Kampmann^{8,23}, #^Ofer Levy^{6,7} & #^Tobias R. Kollmann³**



- 2. Increase host defense
 - Increase (improve) newborn vaccination
 - How does the newborn respond to a successful vaccine (e.g. Hepatitis B, BCG (OPV))?

EPIC & HVP will produce the insight we need 😊





Given most newborns infectious deaths happen in resource constraints areas, interventions have to be feasible (implementable) and low cost.

We need ways to

- broadly increase host protection against many different (even unknown!) pathogens with an intervention given at birth (most likely contact with medical provider) (Olusanya *Health Res Policy Syst* 2010;8:1; Kumar *J Health Popul Nutr* 2010;28(3):300–4)
- easy to implement & to sustain
- cheap (i.e. beyond cost-effective)
- widely & rapidly available

Paradigm Shift! From Pathogen to Host

1. Off-target effects of vaccines
2. Probiotics

Paradigm Shift! From Pathogen to Host

1. **Off-target effects of vaccines**
2. Probiotics

Harnessing the beneficial heterologous effects of vaccination

Helen S. Goodridge, S. Sohail Ahmed, Nigel Curtis, Tobias R. Kollmann, Ofer Levy, Mihai G. Netea, Andrew J. Pollard, Reinout van Crevel and Christopher B. Wilson

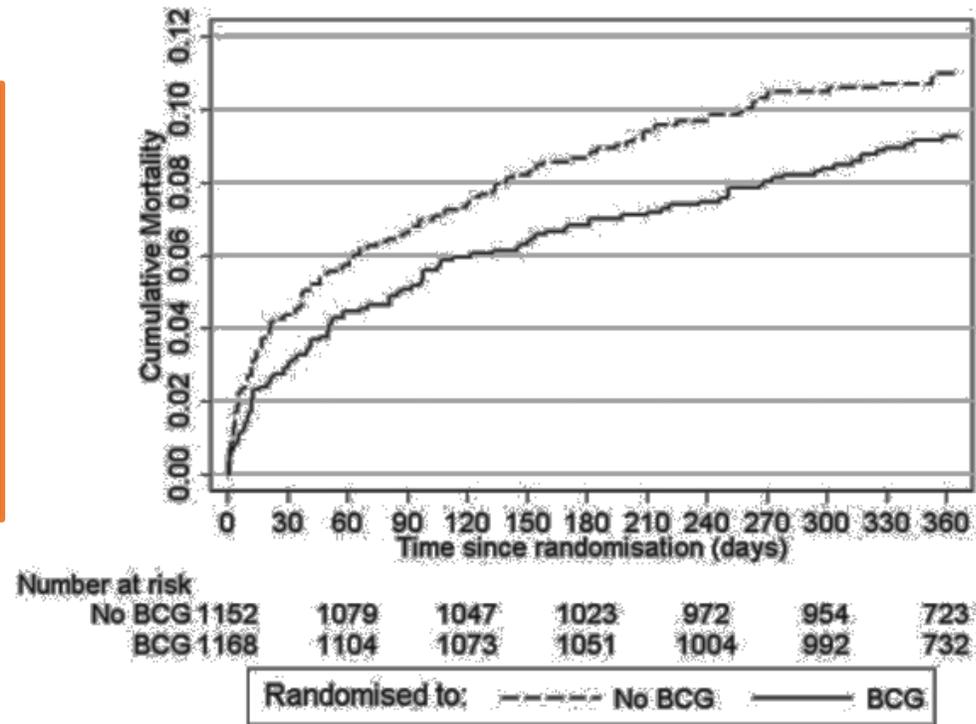
1. Off-target effects of vaccines

- Immunization remains the most effective means by which to reduce global burden of death from infectious disease.
- Classically, a ***disease-centered approach***: designing vaccines to combat the most dangerous pathogens
- Immunizations can influence global health burden in ways *unrelated* to the pathogens they are designed to protect against: a ***host-centered approach***

Bacillus Calmette Guerin

Randomized clinical trial for BCG-mediated NSE in low-birth-weight infants chosen to receive BCG at birth or 6 weeks :

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





J Infect Dis. 2018 Sep 18.

J Pediatric Infect Dis Soc. 2018 Apr 7



Pathogen to Host Paradigm Shift: Summary

1. Many neonatal deaths are due to infections.
2. Despite success in reducing exposure, increasing breastfeeding and pathogen-specific vaccines, neonates still disproportionately suffer and die
3. **Off-target effects of live vaccines such as BCG can broadly reduce neonatal mortality.**

Paradigm Shift! From Pathogen to Host

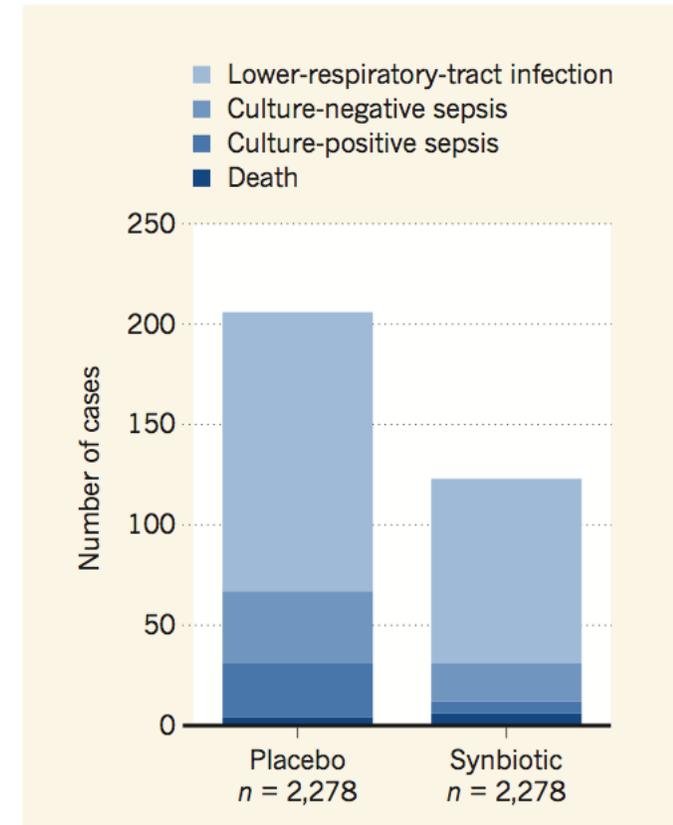
1. Off-target effects of vaccines
2. **Probiotics**

Early-Life Host–Microbiome Interphase: The Key Frontier for Immune Development

Nelly Amenyogbe^{1}, Tobias R. Kollmann^{2†} and Rym Ben-Othman^{2†}*

A randomized synbiotic trial to prevent sepsis among infants in rural India

Pinaki Panigrahi^{1,2}, Sailajanandan Parida³, Nimai C. Nanda⁴, Radhanath Satpathy⁵, Lingaraj Pradhan⁶, Dinesh S. Chandel⁷, Lorena Baccaglini¹, Arjit Mohapatra⁵, Subhranshu S. Mohapatra⁵, Pravas R. Misra⁵, Rama Chaudhry⁸, Hegang H. Chen⁹, Judith A. Johnson¹⁰, J. Glenn Morris Jr¹⁰, Nigel Paneth¹¹ & Ira H. Gewolb¹²





Pathogen to Host Paradigm Shift: Summary

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2. Despite success in reducing exposure, increasing breastfeeding and pathogen-specific vaccines, neonates still disproportionately suffer and die
3. Off-target effects of live vaccines such as BCG can broadly reduce neonatal mortality.
4. Probiotic interventions around birth can reduce risk of NEC in premies, and sepsis as well pneumonia and diarrhea in term infants.

OVERALL SUMMARY

- Neonatal infectious mortality remains high, especially in resource limited settings
- Interventions that focus on the neonatal host rather than specific pathogens and protect against many threats at the same time are needed.
- Host-focused interventions that are cheap and easy to implement and available right now are
 - Off-target effects of live vaccines (BCG)
 - Probiotics (*L. plantarum*)

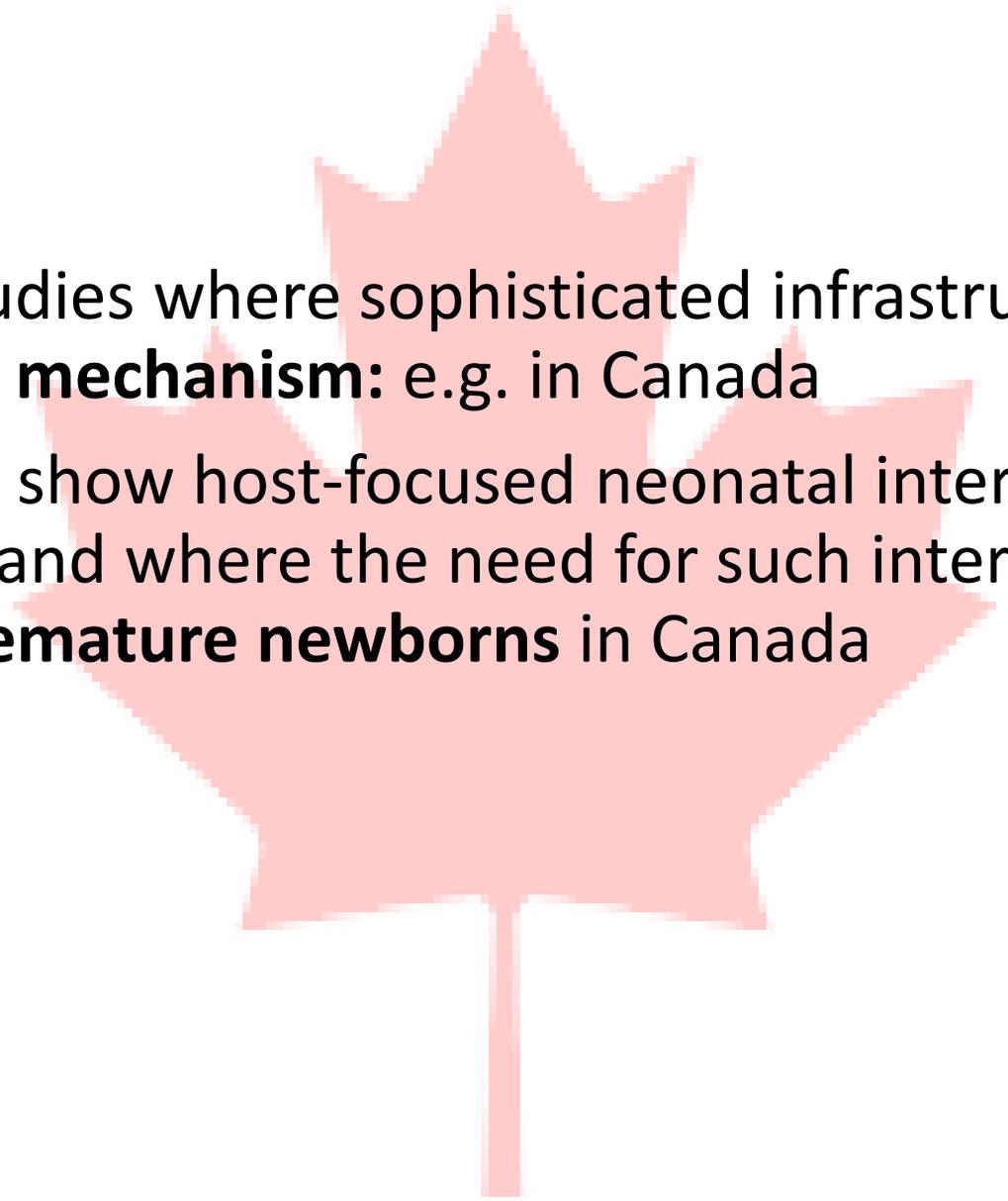
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NEXT STEPS

- conduct these studies where sophisticated infrastructure exists to study and dissect **mechanism**: e.g. in Canada
- data is needed to show host-focused neonatal interventions work where it matters and where the need for such interventions is recognized: in **premature newborns** in Canada



Thank You!

Saving Newborn Lives Through a Paradigm Shift
from a
Focus on the Host *in addition to* Pathogens

tkollm@mac.com



