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Natural Killer T cells are altered in Malawian Infants Immunized with a neonatal RV3-BB rotavirus vaccine: Immune Development Study

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Outline

- Immune development study
- Key research questions
- Aims and Objectives
- Study Design and Methods
- Conclusions

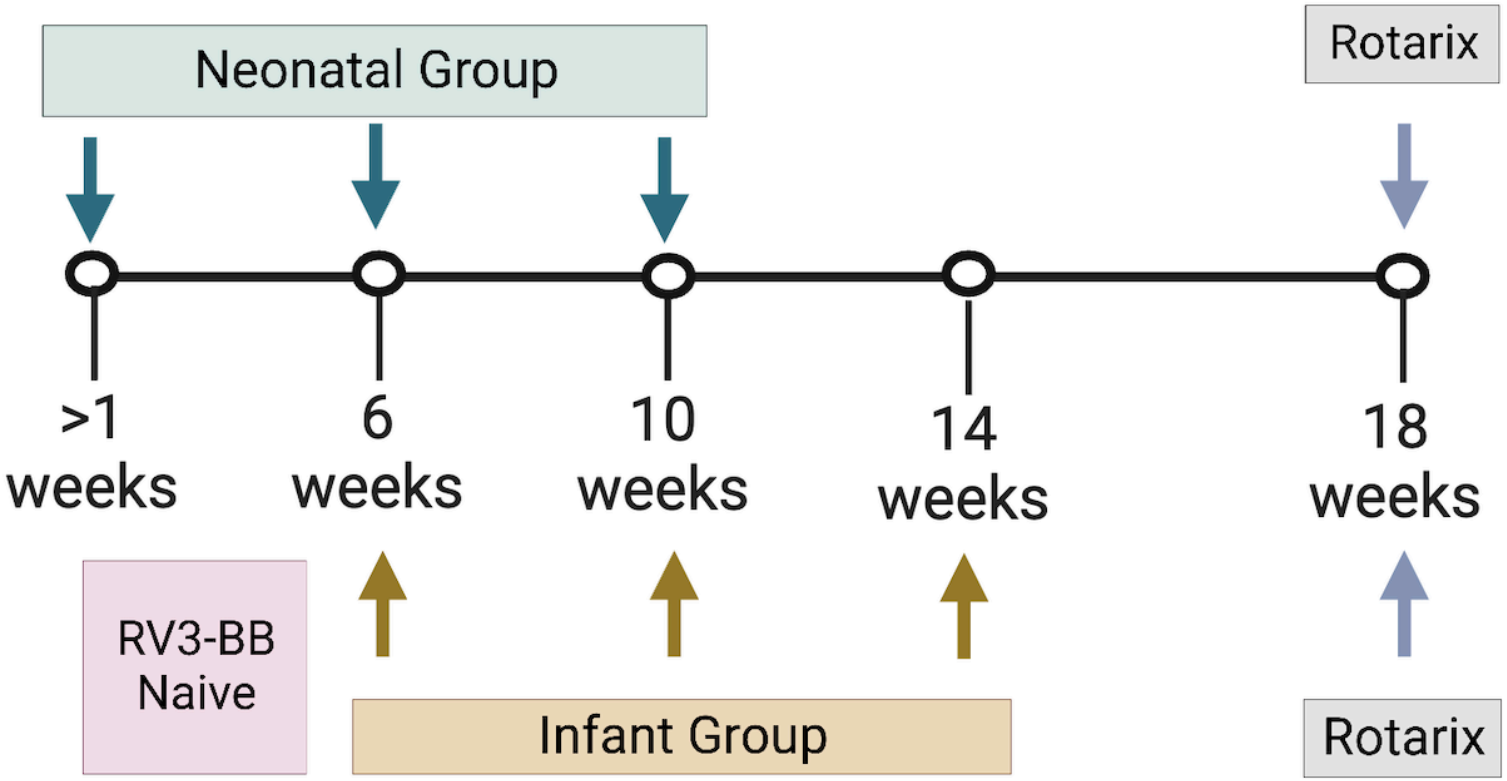
Background

- Vaccines are key interventions with potential to save millions of vulnerable lives
- Some evidence suggests off-target effects of vaccines[1]
- Males and Females are impacted differently by vaccine effects[2]
- It is not known how rotavirus vaccines would impact the developing immune system when administered at birth

(Freyne et al; 2018), [1] (Flanagan et al;2015)[2]

Immune Development Study (IDS)

IDS was an exploratory study within the RV3-BB Safety and Immunogenicity Dose-ranging trial (2018-2020)



Key Research Questions

- What are the developmental changes in innate cells among participants vaccinated with RV3-BB and RV3-BB naive?
- Does a neonatal schedule exhibit a unique cytokine responsiveness following all doses of RV3-BB vaccine?(birth-18weeks)
- Does cytokine responsiveness to innate antigens differ between males and females?

Study aim

To investigate the impact of a neonatal rotavirus (RV3-BB) vaccine on the development of infant innate immune system

Specific objectives

1. To investigate developmental changes of innate cells and cytokine responsiveness in infants administered with a neonatal RV3-BB dose and RV3-BB naïve infants at 6 weeks age
2. To describe innate cytokine responsiveness in Infant schedule and neonatal schedule following all doses of RV3-BB
3. To investigate whether innate cytokine responses are different between males and females

Characteristics of Innate cells and cytokines

- Natural Killer cells

-CD56Dim (Cytotoxic): Decline with age
-CD56Bright (Cytokine producers): Increase with age

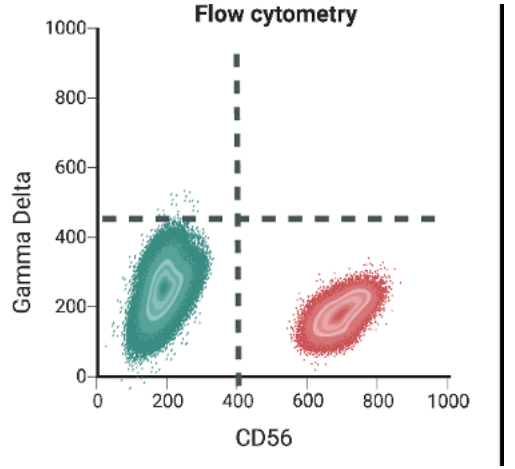
- Natural Killer T cells: Decline with age
- Gamma delta T cells: Increase with age
- Pro-inflammatory cytokines: IFN-g, TNF-A, IL-1B, IL-6 
- Anti-inflammatory cytokines: IL-10 

Methods

Neonate Group
N=92

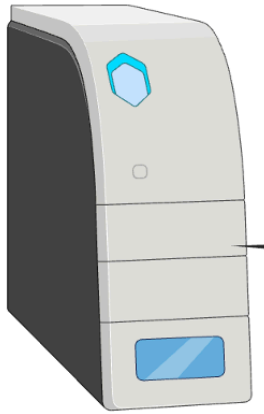
Infant Group
N=47

Flow Cytometry
12 antibody
panel
innate immune
signals

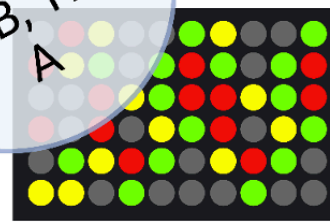


Stimulants
S.pneumonia (SP)
S.aureus (SA),
L.monocytogenes(LM), LPS,
C.albicans, CLO75,
E.coli (EC)

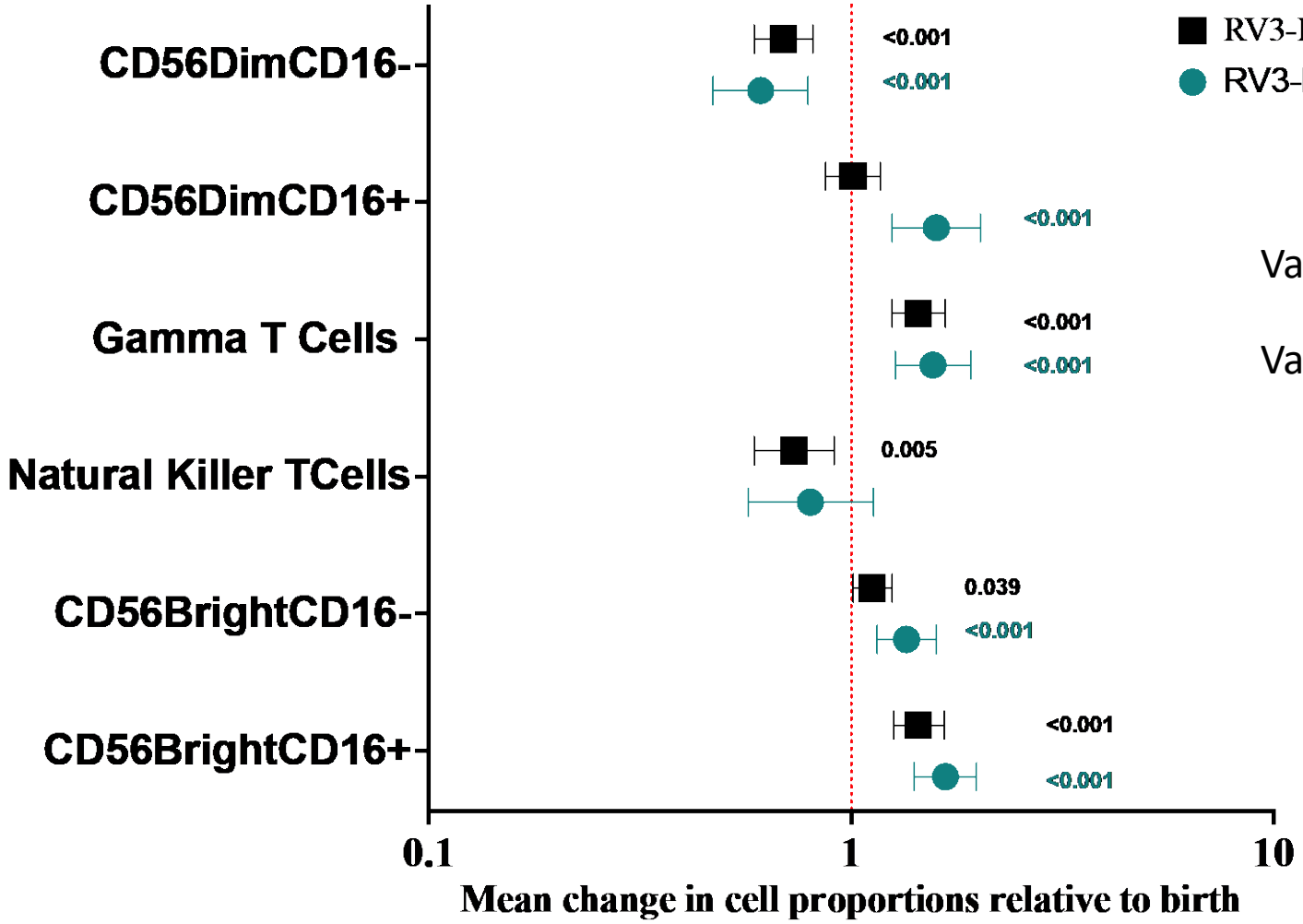
Stimulate WB
with antigens to
common childhood
infections



IFN-g,
IL-10, IL-6,
IL-1B, TNF-
A



Developmental changes of innate cells from birth to 6weeks of age in participants who received a dose and in participants who did not

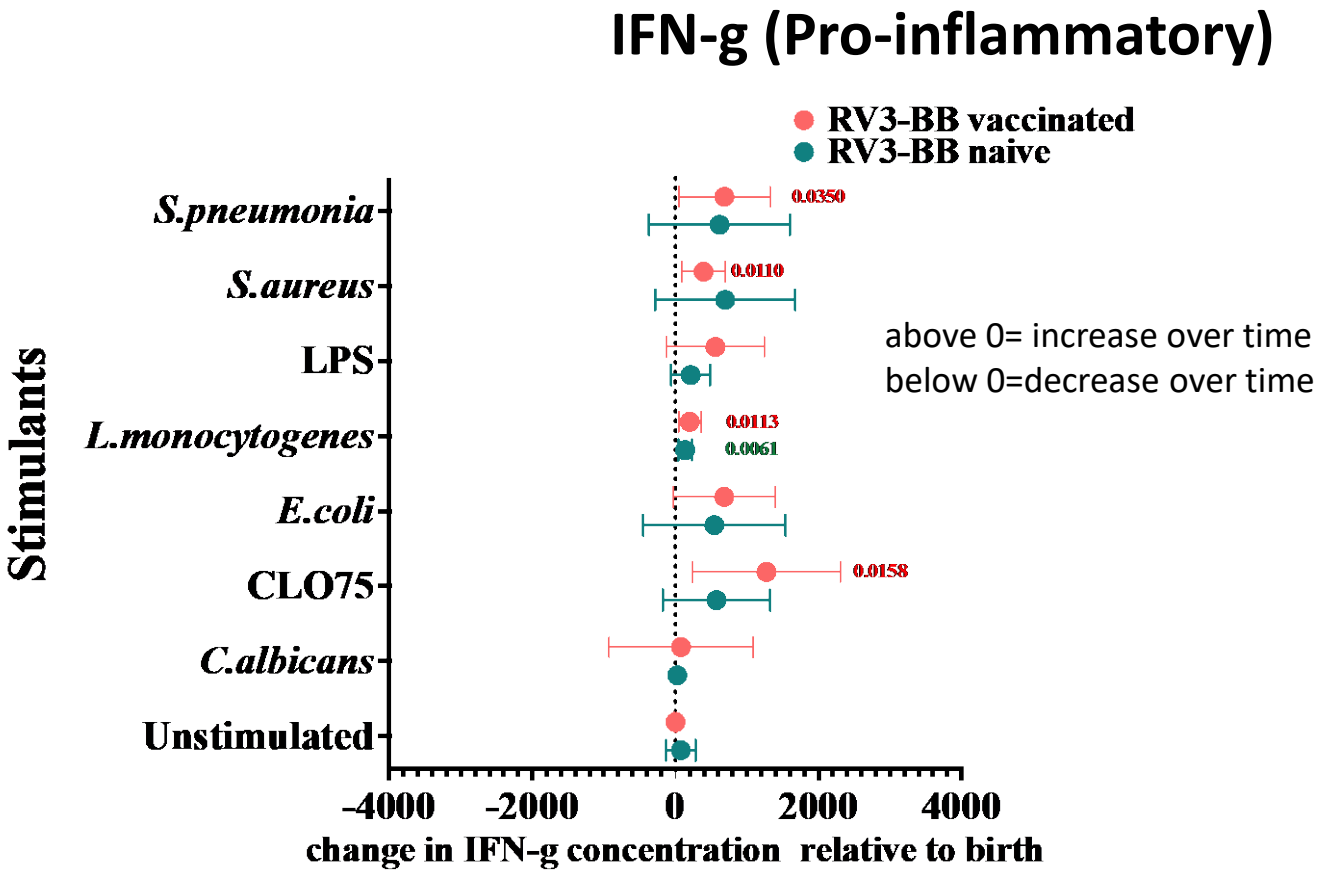


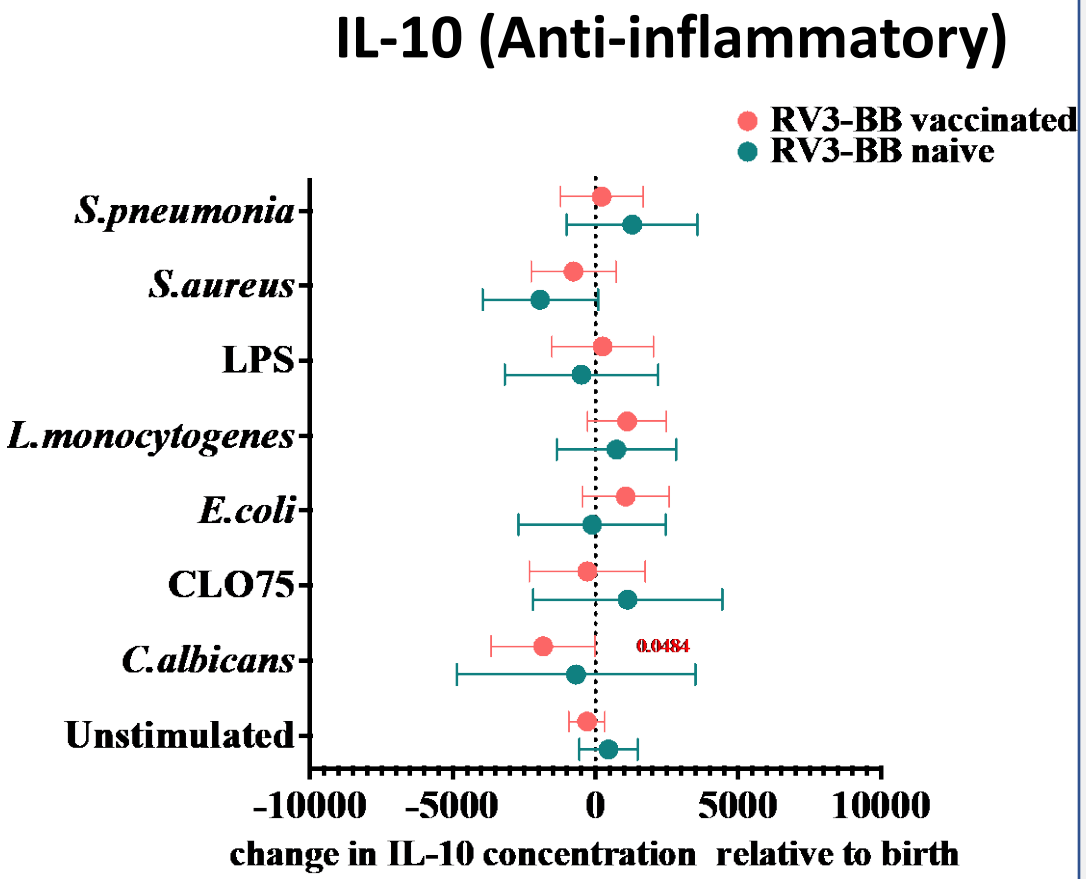
Values above 1=increase over time

Values below 1=decrease over time

- Both vaccinated and RV3-BB naïve participants exhibit expected developmental changes for majority of the cells
- Significant NK T cell reduction in vaccinated group, no significant changes in the CD56DimCD16+

Changes in cytokine responses from birth to 6weeks of age in participants who received a dose and in participants who did not

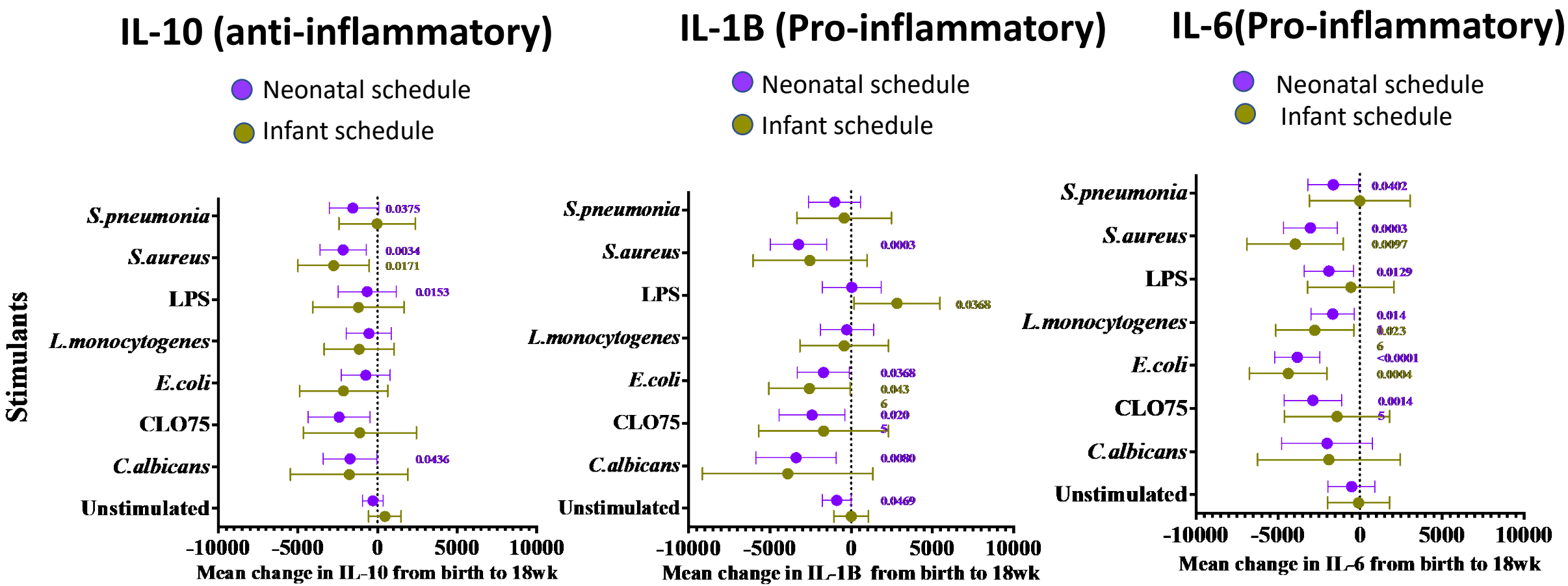




Significantly enhanced IFN-g to SP, SA, LM, CLO75 in the RV3BB vaccinated group but only in LM in the RV3-BB naïve group

Diminished IL-10 to candida but not the other stimuli

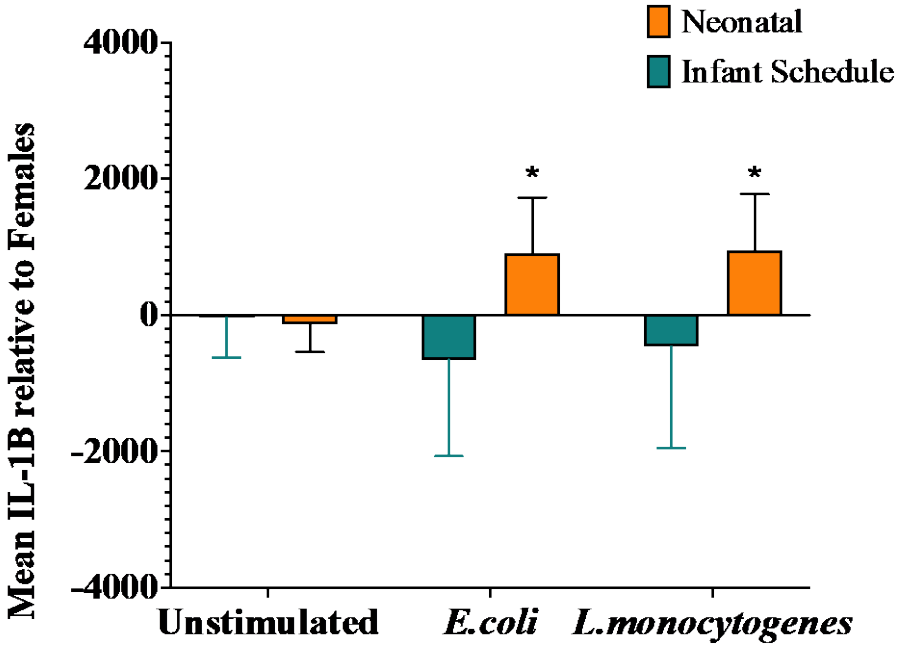
Changes in cytokine responsiveness between birth to 18 weeks in participants receiving RV3-BB in the Neonatal and in the Infant schedule



Significant IL-10 reduction to SP, SA, LPS, CA in Neonatal group but only SA in Infant group. Unexpectedly, pro-inflammatory responses decline across several antigens in both groups and enhanced IL-1B to LPS was observed only in Infant group

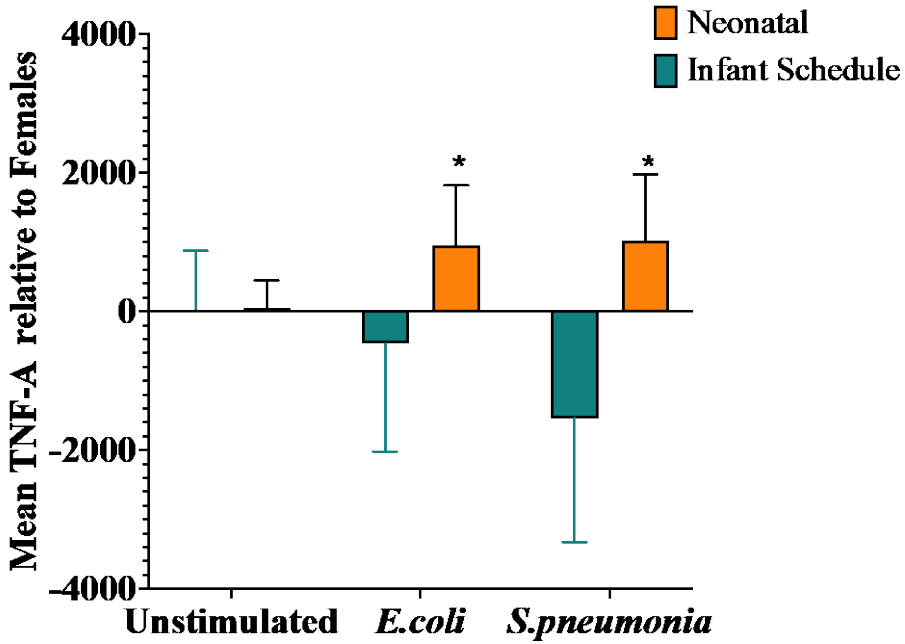
Pro-inflammatory responses (IL-1B and TNF-A) are significantly enhanced in Males compared to Females within Neonatal schedule group

IL-1B responses in Males vs Females



above 0= higher in Males
below 0= Lower in Males
Asterisk=significant difference

TNF-A responses in Males vs Females



Males exhibit enhanced IL-1B and TNF-A in response to heterologous pathogens in Neonatal schedule group

Conclusions

- Significant developmental immune cell proportional changes between birth to 6 weeks of age demonstrate immune maturation.
- Enhanced IFN-g responses in the vaccinated cohort across multiple stimuli is a promising finding in the context of early vaccination.
- Sex differential cytokine responsiveness add to the growing evidence suggesting sex as an important biological confounder.
- Analysis is ongoing to link these findings to beneficial or non-beneficial off-target vaccine effects.

vaccines

MDPI

Review

Leveraging Beneficial Off-Target Effects of Live-Attenuated Rotavirus Vaccines

Prisca Benedicto-Matambo [1,2,3], Julie E. Bines [4], Chikondi Malamba-Banda [1,2,3,5], Isaac T. Shawa [1,3], Kayla Barnes [1,6], Arox W. Kamng'ona [1,7], Daniel Hungerford [2,8], Kondwani C. Jambo [1,9], Miren Iturriza-Gomara [2,8,10], Nigel A. Cunliffe [2,8], Katie L. Flanagan [11,12,13] and Khuzwayo C. Jere [1,2,3,8,*]

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