Vaccination in the NICU and its impact on infection outcomes

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Objectives

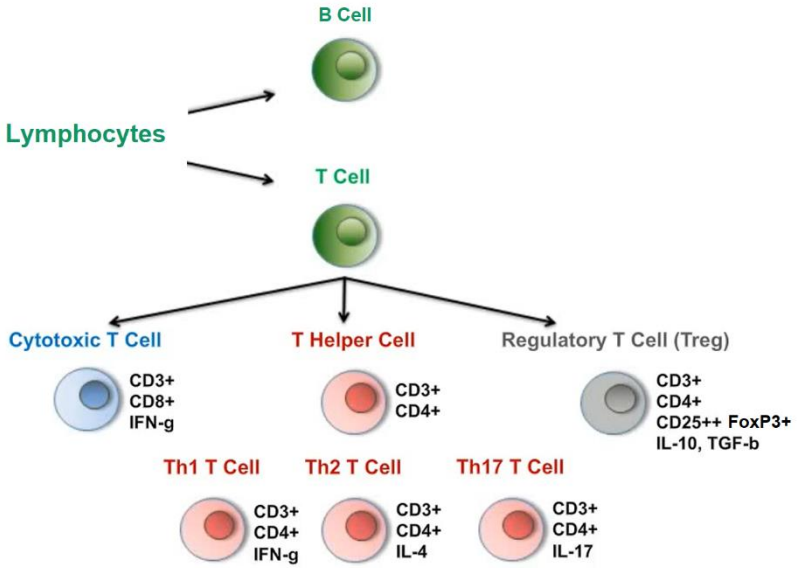
- Newborn immunity in relation to vaccination
- Vaccination of preterm babies
- Improving vaccination rates in preterm babies

- Non-specific effects of vaccination
- Maternal immunisation
- Adjuvants
- The microbiome and vaccination

- No conflicts of interest

Newborn immune system

- Distinct features (vs. "immature")
- All subsets of adaptive immunity are affected



- Memory T cell population is being established
- Multiple boosters required

- Few vaccines are given in the first month of life (BCG, polio, hepatitis B) when the infection risk is greatest
- Several of the effects of vaccination rely on the innate immune system, therefore chronologic age at vaccination should be taken into account rather than gestational age

Preterm babies

- Vaccines are safe and immunogenic
- Increased infection risk – up until adolescence (1.5-4 fold rehospitalization rate due to infection)
- Immunisation is often delayed or deferred
- Higher likelihood of subsequent immunisations being delayed or missed

- Lack of parental/staff understanding of immunity
- Lack of consent
- Being too small or "unwell"
- Other procedures

Tolerability in preterm babies

- Similar to term infants
- Fever – eg. prophylactic paracetamol with meningococcal B
- Methodologic limitations of studies on relationship between vaccination and cardiorespiratory events
- RCT of DTaP vaccination: 93 infants with mean GA of 27 wks, comparable non-vaccinated control group (n=98): no differences in 48 hrs post vaccination (2008, Carbone et al.)
- Monitoring for cardiorespiratory events 48-72 hrs after vaccination is recommended if BW <1000g or GA <29wks
- Vaccine doses should not be split or adjusted for BW or GA. However, when multiple simultaneous injections are not possible in preterm infants because of limited injection sites, vaccines can be administered one at a time on consecutive days

Improving preterm vaccination rates

- Staff/parent education
- Access to evidence-based resources
- Consent obtained in a timely manner
- Reminders in medical record
- Planning of vaccination timing in relation to other procedures (e.g. ROP screening) – set day of the week
- Careful assessment of current clinical status and stability

- Close monitoring
- Guidelines for management of post-immunisation changes

Areas of evolving interest

- Non-specific effects of vaccination: lessons learnt from BCG
- Maternal immunisation: a double-edged sword?
- Adjuvants: enhancing the vaccinal antigen response
- An old friend: the microbiome
- mRNA technology
- Circadian rhythm: no difference in cardiorespiratory events between morning and evening primary vaccination in preterm infants

Non-specific effects

- Few vaccines are given in the first month of life (BCG, polio, hepatitis B) when the infection risk is greatest
- Pathogen-agnostic
- Value in resource-limited settings and during pandemics
- BCG can boost both Th1- and Th2-type responses to other vaccines (hepatitis B and OPV) - established strategy in several countries

- Administration of BCG vaccine at birth in Guinea-Bissau led to a 41% reduction in all-cause mortality at 12 months among VLBW neonates

Non-specific effects - mechanisms

- Trained immunity (innate immune memory):
  - cell maturation through epigenetic and metabolic changes in monocytes, dendritic cells and natural killer cells
- Cross-reactivity of T cells
- Emergency granulopoiesis

- Is it present in a developed country setting? (Williamson et al. 2021)
- BCG group (n=37) and non-BCG group (n=62)
- BCG on day 1, blood sample on day 5 (2-10)
- Emergency granulopoiesis was only present in boys

Maternal immunisation

- Placental transfer (IgG) - not sufficient before 28-30wks
- Breastmilk transfer (IgA)
- Tetanus, pertussis, influenza vaccines are safe and reduce disease-specific morbidity and mortality in the offspring by up to 90%
- Lower level of antibodies against measles in preterm than term
- Is the antigen specificity of IgA conserved vertically?
- However, the presence of maternal antibodies may also interact with vaccine antibody responses early in life (both priming and booster doses)
- Mechanisms: epitope masking, prevention of the differentiation of B cells into plasma cells and memory B cells in the germinal centres
- Microchimerism

Adjuvants

- E.g. aluminum-based mineral salts, oil-in-water emulsions, virosomes

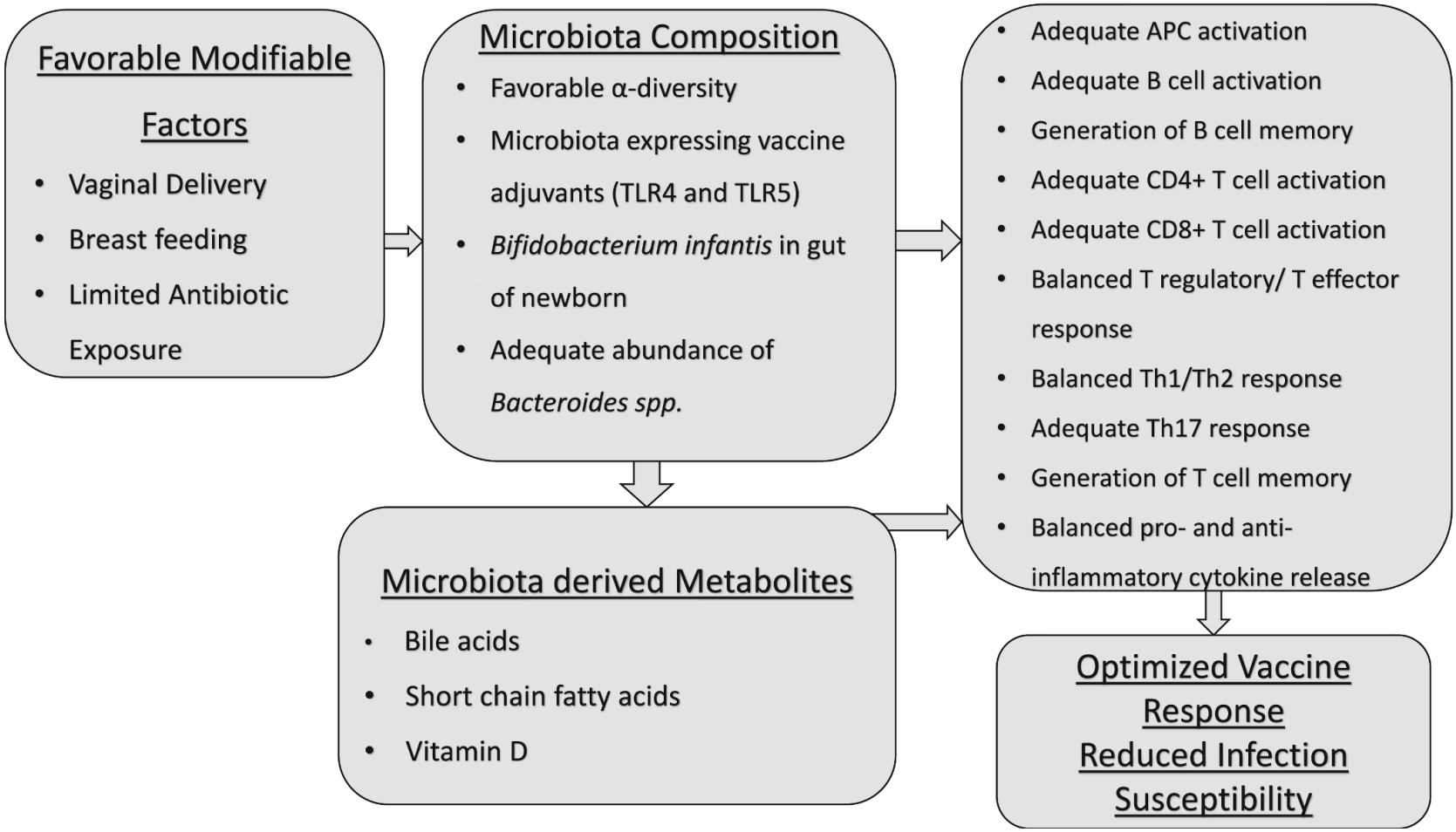
- Elicit beneficial nonspecific innate immune memory responses
- Promote affinity-maturation pathways in T and B cells and memory T and B cell formation
- Increase the half-life of vaccinal antigen
- Enhance the interaction with antigen presenting cells
- Increase mucosal responses

- Target area for precision medicine

Modulation of the microbiome

- Natural source of adjuvants (e.g. SCFAs)
- Antibiotic-treated or germ free mice have diminished antibody production following influenza or polio vaccination compared to normal controls
- Early life treatment of mice with antibiotics led to impaired antibody responses against vaccines which was rescued by fecal microbiota transplantation from age-matched control mice
- In humans, Bifidobacteria support thymic development and correlate with T cell responses against OPV, BCG and tetanus vaccines in the first months of life
- Positive effects on vaccine responses were seen for about 50% of the probiotic formulations, however large heterogeneity (Zimmerman and Curtis, 2018)

Modulation of the microbiome



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Microbiome – oral vaccines

- Oral and parenteral vaccine responsiveness in early life may be improved by promoting intestinal Bifidobacteria and minimizing dysbiosis early in infancy

- In Ghana, oral rotavirus immunogenicity was positively correlated with the relative abundance of Streptococcus bovis and negatively correlated with Bacteroidetes at the time of the first vaccine dose
- Oral rotavirus response among Pakistani infants correlated with a higher relative abundance of Clostridium and Proteobacteria
- Seroconversion rates to oral rotavirus vaccine were significantly lower in Malawi and India than the UK and correlated with dysbiosis

Adverse effects of antibiotics

- Observational cohort study of 560 children in the US (Chapman et al, 2022) between age 6 and 36 months old
- 342 had antibiotic exposures and 218 did not
- Vaccine-induced antibody levels to DTaP and pneumococcal conjugate vaccine antigens were significantly lower in children given antibiotics.
- A higher frequency of vaccine induced antibodies below protective levels in children given antibiotics occurred at 9 and 12 months of age.
- Broader spectrum antibiotics had a greater adverse effect on vaccine-induced antibody levels
- Ten-day versus five-day treatment courses had a greater negative effect.
- Multiple antibiotic courses over time (cumulative antibiotic exposure) was negatively associated with vaccine-induced antibody levels.

Summary

- Several of the effects of vaccination rely on the innate immune system, therefore chronologic age at vaccination should be taken into account rather than gestational age
- No need to delay vaccination in preterm babies for safety concerns, early initiation improves vaccination rates on the long term
- Optimising the microbiome and restoring dysbiosis improves vaccination response

- Individualised approaches taking into account antenatal, feeding and medication history will be necessary in the future