Overcoming the obstacle of scientific knowledge: What do we know about milk immunity and microbiomes?

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I have no conflicts of interest to disclose.

Hyping the immune system

“...a baby’s immune system is at its weakest right after birth” 7

“The importance of breastfeeding cannot be overstated in building a strong immune system.” 4

“Mother’s milk is the Rosetta Stone for all food” 3

“...a ‘made-to-order’ immune-support meal” 3

“...breastfeeding boosts a baby’s immune system...” 5

“Breastmilk is liquid gold, and it’s yours to give!” 6

Quotes from:
Hyping the microbiome

“The Miracle of the Infant Microbiome”¹

Infant Gut Microbiome Associated With Cognitive Development³

“It might be possible to remodel a baby's microbiome”²

 “…microscopic happenings can have lifelong consequences, both for ourselves, our children – and our species as a whole”⁴

Quotes from:

Who knows what?

• Stakeholders:
  • Researchers/scientists
  • Science journalists
  • Health policymakers
  • Informed professionals
  • Uninformed professionals!!
  • Parents
  • The public/society

And, the infants themselves
What is the truth?

- Infant immune systems: weak or not?
- How does milk immunity work?
- How does birth and milk affect infant microbiomes?

1. Are infant immune systems weak?

- Infant immune systems are functional but naïve before birth
  - This means they work, but they’re immature

- Begin maturation upon contact with microbes
  - Birth, skin, kissing, other people, households, pets, crawling, weaning foods

- Risk of harm depends on how virulent the microbe is
1. Are infant immune systems weak?

Other factors can modify how the immune system works


1. Are infant immune systems weak?

- Infants are protected by what scientists call “passive immunity” from their mothers
- Maternal IgG is transferred to fetus – extends protection through 6 months
- Also protected via IgA in milk
1. Are infant immune systems weak?

- "Weak/strong" is the wrong terminology to use!
- "So? Who cares?"
  - Can lead laypeople to the wrong conclusions about how immune systems work ("strong" immune responses have their own set of problems)
  - Lead them to think that exposure to any microbe is a positive, when actually the virulence/harm associated with exposure is not equally distributed among microbes
  - Can lead them to think that multiple vaccinations at one time can "overload" an infant immune system — the infant is exposed to many new microorganisms and can handle them, provided they do not cause harm in the form of infection!

2. How does milk immunity work?

"Passive" immunity: The transfer of active antibodies from one person to another

2. How does milk immunity work?

- IgA produced by breasts
- IgA provides specific information about mother’s disease environment to infant
- Concentration of breastmilk IgA is associated with higher protection

- Immunoglobulin A (~10% total protein)
- Lactoferrin – binds to iron
- Lysozyme – anti-bacterial enzyme

<table>
<thead>
<tr>
<th>Protein</th>
<th>Human Milk (g/l)</th>
<th>Bovine Milk (g/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casein</td>
<td>2.5</td>
<td>27.3</td>
</tr>
<tr>
<td>Whey protein</td>
<td>6.4</td>
<td>5.8</td>
</tr>
<tr>
<td>α-Lactalbumin</td>
<td>2.6</td>
<td>1.1</td>
</tr>
<tr>
<td>Lactoferrin</td>
<td>1.7</td>
<td>trace</td>
</tr>
<tr>
<td>θ-Lactoglobulin</td>
<td>-</td>
<td>3.6</td>
</tr>
<tr>
<td>Lysozyme</td>
<td>0.5</td>
<td>trace</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Immunoglobulin A</td>
<td>1.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Immunoglobulin G</td>
<td>0.03</td>
<td>0.6</td>
</tr>
<tr>
<td>Immunoglobulin M</td>
<td>0.02</td>
<td>0.03</td>
</tr>
</tbody>
</table>
2. How does milk immunity work?

- Wide range of cytokines, chemokines, cytokine receptors, cytokine receptor antagonists
- Give sense of activity of cells
- Generally anti-inflammatory in milk

Values from Agarwal et al. 2011 *J Hum Lact*, 27. Mature mil, ELISA values only

2. How does milk immunity work?

- Values vary wildly between populations
- Little is known about their effects, short term or long term

<table>
<thead>
<tr>
<th></th>
<th>U.S. Mean (S.D.) or % (n = 74)</th>
<th>Kenya Mean (S.D.) or % (n = 233)</th>
<th>T-value (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foremilk fat (g/dL)</td>
<td>3.6 (1.6)</td>
<td>2.7 (1.4)</td>
<td>4.3 (&lt;0.0001)</td>
</tr>
<tr>
<td>TGF-β2 (pg/mL)</td>
<td>736.4 (48.0)</td>
<td>74.8 (16.8)³</td>
<td>13.9 (&lt;0.0001)</td>
</tr>
<tr>
<td>sTNF-aRI (pg/mL)</td>
<td>685.0 (27.5)</td>
<td>831.9 (15.6)</td>
<td>2.7 (0.008)</td>
</tr>
<tr>
<td>sTNF-aRII (pg/mL)</td>
<td>839.1 (21.1)</td>
<td>1151.4 (15.7)</td>
<td>6.8 (&lt;0.0001)</td>
</tr>
<tr>
<td>IL-1ra (pg/mL)</td>
<td>532.4 (100.1)</td>
<td>192.6 (17.0)²</td>
<td>4.2 (&lt;0.0001)</td>
</tr>
</tbody>
</table>
2. How does milk immunity work?

- So what?
  - We know that the basic mechanisms of “passive immunity” only last as long as an infant is nursing
  - Dose-response of breastfeeding is established, but not dose of milk immunity (subtle difference)
  - The long-term effects are likely, but not clear
  - Immunological messengers called cytokines may play a longer-term role, but their function in infant bodies are not well-established

3. Birth, milk, and infant microbiomes

- Common wisdom: vaginal versus C-section delivery creates drastically different microbiomes in infants
- Delivery differences found at birth only in mouth and skin
- “We conclude that within the first 6 weeks of life, the infant microbiota undergoes substantial reorganization, which is primarily driven by body site and not by mode of delivery.”
3. Birth, milk, and infant microbiomes

- Probiotic use in adults is transient
- In infants, one strain can potentially persist in the microbiome
- The supplemented bacteria use human milk oligosaccharides to survive

Note: study was funded by company manufacturing this supplement

Persistence of Supplemented *Bifidobacterium longum* subsp. *infantis* EVC001 in Breastfed Infants

Davies A. Pressey, Andrea A. Proctor, Lesley M. Cunningham, Claire A. Story, Michelle C. Palachuk, George Cavanagh, Sege Xu, Jasmine C. C. Davis, Carla D. Lotzke, Bethany M. Hendrick, Samina I. Pressey, Darla Barke, J. Denise Gossan, David A. Miller, Jessica F. Snoddy, Blair A. Underwood

DOI: 10.1128/mSphere.00191-17

3. Birth, milk, and infant microbiomes

- Does milk “seed” infant microbiomes?
- “During the first 30 days of life, infants who breastfed to obtain 75% or more of their daily milk intake received a mean (SD) of 27.7% (15.2%) of the bacteria from breast milk and 10.3% (6.0%) from areolar skin.”

July 2017

Association Between Breast Milk Bacterial Communities and Establishment and Development of the Infant Gut Microbiome
3. Birth, milk, and infant microbiomes

- Do infants “order” their milk immunity?
- Original idea based on paper that showed (via ultrasound) that saliva might make its way into the breast via reversal of milk flow
- People ran with this, suggesting that microbes in saliva might stimulate immune cells in mammary glands and produce milk

![Ultrasound Imaging of Milk Ejection in the Breast of Lactating Women](image)

Donna T. Ramsay, Jacqueline C. Kent, Robyn A. Owens, Peter E. Hartmann

3. Birth, milk, and infant microbiomes

- Very little information exists using next generation sequencing (NGS)
- One paper has sequenced 10 infant saliva samples vs. 10 mothers’ milk samples.
- “No statistically significant relationships were observed between maternal and child microbiomes”—but, were methods adequate?

![Bacterial microbiome of breast milk and child saliva from low-income Mexican-American women and children](image)

Veronica Cruz, Kelly Streat, Stephen Franko, Ava Bouchard, Lee Riley, Brenda Enriquez, and Nina Millard
3. Birth, milk, and infant microbiomes

- Sequencing is ongoing: ~250 infant salivary microbiomes with some matching milk samples from rural Kenya (age 2 weeks – 25 months)
- Initial investigations show salivary *Streptococcus* abundance in line with Dave et al. 2016
- Unlike other studies, we have found very low levels of bacterial DNA in milk
- Next steps: apply new methods for comparison

3. Birth, milk, and infant microbiomes

- Takeaway: we do not know 100% what a healthy infant microbiome is!
- Attempts to modify it are based on adult science on probiotics
- Breastfeeding from the nipple is the best “default” recommendation based on available science
Questions?

• What questions have you gotten from parents/the public?

• What questions do you have?

• What kinds of misinformation have you heard?