PROBIOTICS IN CHILDREN

H. Szajewska (PL)
<table>
<thead>
<tr>
<th>Faculty Disclosure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No, nothing to disclose</strong></td>
</tr>
<tr>
<td><strong>Yes, please specify:</strong></td>
</tr>
</tbody>
</table>

HS has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for:

- Arla,
- BioGaia,
- Biocodex,
- Danone,
- Dicofarm,
- Nestlé, NNI
- Nutricia,
- Mead Johnson.
Probiotics in children

Prof. Hania Szajewska
The Medical University of Warsaw
Department of Paediatrics
‘When I was young I thought that money was the most important thing in life; Now, that I am old, I know that it is true….’

Oscar Wilde
The probiotic market is growing rapidly, with no signs that it will be slowing down.
Probiotics: myth or miracle?

Are probiotics really that good for your health?

Probiotics: panacea or just a big ‘fad’?
Probiotics labelled 'quite useless'

Probiotics 'not as beneficial for gut health as previously thought'

Are Probiotics Money Down the Toilet? Or Worse?

Jennifer Abbasi
Two gut microbiota studies questioned probiotic health benefits

Probiotics transiently colonize the human gut mucosa in highly individualized patterns

Probiotics perturb rather than aid in microbiota recovery back to baseline after antibiotic treatment in humans.
Two RCTs Published in NEJM

Lactobacillus rhamnosus GG versus Placebo for Acute Gastroenteritis in Children


Multicenter Trial of a Combination Probiotic for Children with Gastroenteritis


Probiotics No Better Than Placebo for Acute Gastroenteritis.
What are probiotics?

• Updated (2014) definition
  – Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host

Examples
  ▪ Lactobacilla
  ▪ Bifidobacteria
  ▪ S boulardii
Mechanism of action of probiotics

- **Rare**
  - Strain-specific effects
    - Neurological effects
    - Immunological effects
    - Endocrinological effects
    - Production of specific bioactives

- **Frequent**
  - Species-level effects
    - Vitamin synthesis
    - Direct antagonism
    - Gut barrier reinforcement
    - Bile salt metabolism
    - Enzymatic activity
    - Neutralization of carcinogens

- **Widespread**
  - Among studied probiotics
    - Colonization resistance
    - Acid and SCFA production
    - Regulation of intestinal transit
    - Normalization of perturbed microbiota
    - Increased turnover of enterocytes
    - Competitive exclusion of pathogens

*Nature Reviews | Gastroenterology & Hepatology*
How to choose a probiotic?

- Genus, species, strain
- Expiration date
- Storage needs
- Dose
- Formulation
- Evidence

ISAPP 2017
# Genus, species, strain

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Strain</th>
<th>Culture collection</th>
<th>Marketing name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus</td>
<td>rhamnosus</td>
<td>GG</td>
<td>ATCC 53103</td>
<td>LGG</td>
</tr>
<tr>
<td>Lactobacillus</td>
<td>reuteri</td>
<td></td>
<td>DSM 17938</td>
<td>L reuteri</td>
</tr>
<tr>
<td>Saccharomyces</td>
<td>boulardii</td>
<td></td>
<td>CNCM I-745</td>
<td>Enterol</td>
</tr>
</tbody>
</table>
Not all probiotics are created equal

The efficacy and safety of each probiotic should be evaluated separately
How to choose a probiotic?

- **Genus, species, strain**
- **Expiration date**
- **Storage needs**
- **Dose**
- **Formulation**
- **Evidence**

ISAPP 2017
Are refrigerated products better than non-refrigerated?
Expiration date & Storage needs

• The stability of the live microbes in a probiotic product depends on conditions of storage.

• Some products may require refrigeration, but others do not.

• Responsible product manufacturers make certain that their probiotic is able to meet its label claim through the end of shelf-life if stored as recommended.
How to choose a probiotic?

- Genus, species, strain
- Expiration date
- Storage needs
- Dose
- Formulation
- Evidence
Is a higher dose and greater number of strains better?

• Not necessarily!

• Use products that have been tested in human studies with positive outcomes for the benefit you are interested in.
How to choose a probiotic?

- Genus, species, strain
- Expiration date
- Storage needs
- Dose
- Formulation
- Evidence

ISAPP 2017
Examples
Is it better to take probiotics as supplements or foods?

- Human trials have shown benefits for both food and supplement forms of probiotics.
- No comparative trials have been conducted suggesting one format is better than the other.
How to choose a probiotic?

- **Genus, species, strain**
  - Lactobacillus plantarum AB2
  - Lactobacillus rhamnosus CD3
  - Lactobacillus salivarius EF6
  - Bifidobacterium longum ABC

- **Expiration date**
  - Use by 12/12/2018

- **Storage needs**
  - KEEP DRY TO MAINTAIN POTENCY

- **Dose**
  - Colony Forming Units (CFU’s) 100,000,000

- **Formulation**

- **Evidence**
Evidence
## Probiotics – what is the evidence?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effect of probiotics as a group</th>
<th>Probiotics with documented efficacy</th>
</tr>
</thead>
</table>
| **Acute gastroenteritis**          | 1-day reduction in the duration of diarrhea | ESPGHAN/ESPID 2014
|                                    |                                 | LGG
|                                    |                                 | S boulardii
|                                    |                                 | L reuteri DSM 17938 |
| **Prevention of AAD**              | Reduced risk                    | ESPGHAN 2016                        |
|                                    |                                 | LGG                                 |
|                                    |                                 | S boulardii                         |
| **Prevention of nosocomial diarrhea** | Reduced risk                  | ESPGHAN 2018                        |
|                                    |                                 | LGG                                 |
What is new in 2019?

LGG for acute gastroenteritis

Meta-analysis: *Lactobacillus* GG for treating acute gastroenteritis in children – updated analysis of randomised controlled trials

H. Szajewska, A. Skórka, M. Ruszczyński & D. Gieruszczak-Białek

Szajewska et al. Aliment Pharmacol Ther 2019
LGG vs. control
Duration of diarrhea

16 RCTs, n=3946
MD -20 h (-27 to -13)
High heterogeneity $I^2$ 98%

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration (h) (95% CI)</th>
<th>Heterogeneity</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nixon 2 x 10^10</td>
<td>2.82 (1.5, 3.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schnadower 2 x 10^10</td>
<td>2.53 (2.45, 2.64)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costa-Ribeiro 1 x 10^10</td>
<td>1.59 (0.16, 1.63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sindhu 1 x 10^10</td>
<td>4.05 (1.6, 5.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritchie 1.5 x 10^10</td>
<td>2.18 (2.44, 2.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basu 2007 1.2 x 10^4</td>
<td>6.8 (2.1, 6.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 2070 (1879) 100.0% -0.83 [-1.13, -0.53]

Heterogeneity: $\tau^2 = 0.32; \chi^2 = 841.17, df = 15 (P < 0.00001); I^2 = 98$
Test for overall effect: $Z = 5.45 (P < 0.00001)$
## LGG vs. control

Duration of diarrhea. Low risk of bias.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>L rhamnosus GG</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Weight</td>
<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>Basu 2009 2x10^10/2x10^12</td>
<td>5.069</td>
<td>1.24</td>
<td>374</td>
<td>7.23</td>
<td>1.27</td>
</tr>
<tr>
<td>Shornikova 1 x 10^10</td>
<td>2.7</td>
<td>2.2</td>
<td>59</td>
<td>3.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Nixon 2x10^10</td>
<td>2.82</td>
<td>1.5</td>
<td>63</td>
<td>3.08</td>
<td>1.64</td>
</tr>
<tr>
<td>Schnadower 2 x 10^10</td>
<td>2.53</td>
<td>2.45</td>
<td>472</td>
<td>2.64</td>
<td>2.3</td>
</tr>
<tr>
<td>Basu 2007 1.2 x 10^8</td>
<td>6.8</td>
<td>2.1</td>
<td>323</td>
<td>6.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1291</td>
<td>1118</td>
<td>100.0%</td>
<td>-0.68</td>
<td>-1.82, 0.45</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 1.61; Chi^2 = 193.51, df = 4 (P < 0.00001); I^2 = 98%

Test for overall effect: Z = 1.18 (P = 0.24)

---

5 RCTs, n=2409

MD -20 h (-16 to 11)

High heterogeneity I^2 98%

Szajewska et al. Aliment Pharmacol Ther 2019

<table>
<thead>
<tr>
<th>Probiotic</th>
<th>RCT</th>
<th>N</th>
<th>Efekt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus rhamnosus GG</td>
<td>16</td>
<td>3949</td>
<td>↓ 20 h</td>
</tr>
<tr>
<td>S. boulardii</td>
<td>5</td>
<td>2409</td>
<td>NS</td>
</tr>
<tr>
<td>Lactobacillus reuteri</td>
<td>4</td>
<td>347</td>
<td>↓ 22 h</td>
</tr>
<tr>
<td>Bacillus clausii O/C, SIN, N/R, and T</td>
<td>7</td>
<td>1107</td>
<td>↓ 12 h</td>
</tr>
<tr>
<td>L. helveticus R0052 &amp; L. rhamnosus R0011</td>
<td>4</td>
<td>1325</td>
<td>NS</td>
</tr>
<tr>
<td>L. rhamnosus 19070 &amp; L reuteri DSM 12246</td>
<td>2</td>
<td>112</td>
<td>↓ 24 h</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td>Various</td>
</tr>
</tbody>
</table>

About 160 RCTs

Stay tuned!

ESPGHAN WG on Probiotics is working on an up-date.
Prevention of antibiotic-associated diarrhoea (AAD)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effect of probiotics as a group</th>
<th>Probiotics with documented efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of AAD</td>
<td>Reduced risk</td>
<td>ESPGHAN 2016</td>
</tr>
<tr>
<td></td>
<td></td>
<td>LGG S boulardii</td>
</tr>
</tbody>
</table>
What is new?
L reuteri DSM 17938 for preventing AAD

Not all probiotic strains are the same.

Probiotics for preterm infants
Probiotics for Preterm Infants: A Strain-Specific Systematic Review and Network Meta-analysis

*Chris H.P. van den Akker, ‡Johannes B. van Goudoever, §Hania Szajewska, §Nicholas D. Embleton, †Iva Hojsak, ‡Daan Reid, and #Raanan Shamir, for the ESPGHAN Working Group for Probiotics, Prebiotics & Committee on Nutrition
Probiotics for preterm infants

51 RCTs, n=11,231

ESPGHAN WG on Probiotics. Van den Akker, van Goudoever, Szajewska et al. JPGN 2018
Upcoming ESPGHAN position paper

Probiotics and preterm infants: a position paper by the ESPGHAN Committee on Nutrition and the ESPGHAN Working Group for Probiotics and Prebiotics
Clinical questions

1. Are probiotics safe enough for administration to preterm infants?
2. Should probiotics be used in preterm infants? If yes, which probiotics (single or combinations) should be used in what dose?
3. Are combinations of species more effective than the use of a single strain to reduce the risk of NEC (stage 2 or 3)?
4. Which dose of a probiotic strain or combination of strains should be administered?
5. What should be the duration of administering probiotics?
6. Is it appropriate to administer other strains than those studied in large well-conducted RCTs?
Clinical questions

1. Are probiotics safe enough for administration to preterm infants?

2. **Should probiotics be used in preterm infants? If yes, which probiotics (single or combinations) should be used in what dose?**

3. Are combinations of species more effective than the use of a single strain to reduce the risk of NEC (stage 2 or 3)?

4. Which dose of a probiotic strain or combination of strains should be administered?

5. What should be the duration of administering probiotics?

6. Is it appropriate to administer other strains than those studied in large well-conducted RCTs?
# Probiotics for prevention of NEC

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th></th>
<th></th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>LGG</strong>&lt;br&gt;1x $10^9$ CFU to 6x$10^9$ CFU</td>
<td></td>
<td></td>
<td><strong>B. breve BBG-001</strong>&lt;br&gt;<strong>S. boulardii</strong></td>
</tr>
<tr>
<td></td>
<td><strong>B. infantis Bb-02, B lactis Bb-12, Str therm TH-4</strong>&lt;br&gt;3.5x$10^8$ CFU (of each strain)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>L. reuteri DSM 17938</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>B bifidum NCDO 1453 &amp; L acidoph NCDO 1748</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Probiotics – what is the evidence?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effect of probiotics as a group</th>
<th>Examples of probiotics with documented or promising efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergy prevention</td>
<td>No effect</td>
<td>WAO 2015 – not recommended</td>
</tr>
<tr>
<td>Eczema</td>
<td>Reduced risk</td>
<td>Likely net benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Conditional recommendations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Very low quality evidence.</td>
</tr>
</tbody>
</table>
### 1.1.1 Pregnant women only

<table>
<thead>
<tr>
<th>Probiotics</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boyle 2011</td>
<td>42</td>
<td>122</td>
<td>47</td>
<td>0.88 [0.63, 1.22]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td>122</td>
<td></td>
<td>0.88 [0.63, 1.22]</td>
</tr>
</tbody>
</table>

Total events: 42, 47

Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)

### 1.1.2 Pregnant +/- BF mothers +/- infants

<table>
<thead>
<tr>
<th>Probiotics</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrahamsen 2007</td>
<td>34</td>
<td>95</td>
<td>32</td>
<td>1.04 [0.70, 1.53]</td>
</tr>
<tr>
<td>Allen 2012</td>
<td>75</td>
<td>220</td>
<td>76</td>
<td>1.05 [0.81, 1.36]</td>
</tr>
<tr>
<td>Dotterud 2010</td>
<td>29</td>
<td>138</td>
<td>48</td>
<td>0.61 [0.41, 0.91]</td>
</tr>
<tr>
<td>Huurre 2008</td>
<td>7</td>
<td>72</td>
<td>12</td>
<td>0.55 [0.23, 1.32]</td>
</tr>
<tr>
<td>Kalliomaki 2001a</td>
<td>15</td>
<td>64</td>
<td>31</td>
<td>0.51 [0.31, 0.86]</td>
</tr>
<tr>
<td>Kim 2010</td>
<td>12</td>
<td>33</td>
<td>22</td>
<td>0.58 [0.34, 0.97]</td>
</tr>
<tr>
<td>Kopp 2008</td>
<td>14</td>
<td>50</td>
<td>12</td>
<td>1.03 [0.53, 1.98]</td>
</tr>
<tr>
<td>Kukkonen 2007</td>
<td>57</td>
<td>459</td>
<td>82</td>
<td>0.70 [0.51, 0.96]</td>
</tr>
<tr>
<td>Marschan 2008</td>
<td>16</td>
<td>52</td>
<td>18</td>
<td>0.79 [0.46, 1.35]</td>
</tr>
<tr>
<td>Niers 2009</td>
<td>23</td>
<td>50</td>
<td>30</td>
<td>0.74 [0.51, 1.07]</td>
</tr>
<tr>
<td>Ou 2012</td>
<td>16</td>
<td>65</td>
<td>16</td>
<td>0.64 [0.47, 0.90]</td>
</tr>
<tr>
<td>Rautava 2002</td>
<td>4</td>
<td>27</td>
<td>14</td>
<td>0.27 [0.09, 0.82]</td>
</tr>
<tr>
<td>Rautava 2012</td>
<td>21</td>
<td>73</td>
<td>44</td>
<td>0.62 [0.28, 1.40]</td>
</tr>
<tr>
<td>Wickens 2008a</td>
<td>23</td>
<td>157</td>
<td>22</td>
<td>0.56 [0.32, 0.95]</td>
</tr>
<tr>
<td>Wickens 2008b</td>
<td>38</td>
<td>158</td>
<td>21</td>
<td>0.64 [0.39, 1.05]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1713</td>
<td>1554</td>
<td>91.5%</td>
<td>0.76 [0.61, 0.93]</td>
</tr>
</tbody>
</table>

Total events: 384, 480

Heterogeneity: Tau² = 0.06; Chi² = 30.03, df = 14 (P = 0.008); I² = 53%
Test for overall effect: Z = 3.88 (P = 0.0001)

### RR 0.72

(0.61 to 0.85)

When to start?  
When to stop?
Lactobacillus GG

No support for the general recommendation to use probiotics for preventing eczema, unless specific strains would be indicated.
## Probiotics – what is the evidence?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effect of probiotics as a group</th>
<th>Examples of probiotics with documented or promising efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile colic – prevention</td>
<td><strong>Reduced crying time</strong></td>
<td>L. reuteri DSM 17938</td>
</tr>
<tr>
<td>Infantile colic – management</td>
<td></td>
<td>L. reuteri DSM 17938 (especially in BF infants)</td>
</tr>
</tbody>
</table>
Infantile colic
Individual participant data meta-analysis

Lactobacillus reuteri to Treat Infant Colic: A Meta-analysis
Valerie Sung, PhD, a Frank D’Amico, PhD, b,c Michael D. Cabana, MD, d Kim Chau, PhD, e Gideon Koren, MD, e Francesco Savino, PhD, f Hania Szajewska, MD, g Girish Deshpande, MSc, h Christophe Dupont, PhD, i Flavia Indrio, MD, j Silja Mentula, PhD, k Anna Partty, PhD, l Daniel Tancredi, PhD m

Sung et al. Pediatrics 2018 Jan;141(1)
Infantile colic
Individual participant data meta-analysis

• **Decreased daily crying time**
  – 25.4 minutes (95% CI 47.3; 3.5)

• **Increased success rate**
  – 28% in the probiotic group versus
  – 9% in placebo group
  – NNT 4
## Other pediatric indications

<table>
<thead>
<tr>
<th>Condition</th>
<th>Probiotic(s)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>H pylori infection</td>
<td>S boulardii, L casei DN 114 001</td>
<td>ESPGHAN – not recommended</td>
</tr>
<tr>
<td>Abdominal pain (IBS)</td>
<td>LGG</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VSL#3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L reuteri DSM 17938</td>
<td></td>
</tr>
<tr>
<td>Ulcerative colitis (induction of remission)</td>
<td>E coli Nissle 1917 VSL#3</td>
<td>ESPGHAN/ECCO</td>
</tr>
<tr>
<td>Crohn’s disease (induction of remission)</td>
<td>ECCO/ESPGHAN – not recommended</td>
<td></td>
</tr>
<tr>
<td>Functional constipation</td>
<td>ESPGHAN/NASPGHAN – not recommended</td>
<td></td>
</tr>
</tbody>
</table>
Safety

Zero risk does not exist
Safety of probiotics
Systematic review of case reports, RCTs and non-RCTs

- Generally safe
- Some probiotic products (strain or combinations) have been shown to increase the risk of complications in specific patient groups.

Bacteriemia & fungemia
Almost all cases
  - immunocompromised patients
  - with central venous catheters
  - severe underlying diseases

Whelan & Myers AJCN 2010;91:687-703
**Conclusion:** Harms reporting in published reports of RCTs assessing probiotics, prebiotics, and synbiotics often is lacking or inadequate. We cannot broadly conclude that these interventions are safe without reporting safety data.
Is quality of probiotics an issue?

- A number of studies have questioned the microbiological quality and labelling of many probiotic products
  - Only some probiotic products meet the definition of probiotics, i.e., contain viable, well-defined microorganisms in sufficient numbers
  - Often products contain other species of organisms

A call for improved quality control (ESPGHAN)

Commercial Probiotic Products: A Call for Improved Quality Control. A Position Paper by the ESPGHAN Working Group for Probiotics and Prebiotics

*Sanja Kolaček, †Iva Hojsak, ‡Roberto Berni Canani, §Alfredo Guarino, ¶Flavia Indrio, ¶Rok Orel, ¶Bruno Pot, ¶Raanan Shamir, ¶¶Hania Szajewska, §§Yvan Vandenplas, ¶¶Johannes van Goudoever, and §§§Zvi Weizman, ESPGHAN Working Group for Probiotics and Prebiotics

The WG recommends choosing a probiotic, from a manufacturer who has a regulated quality control.
**Summary**

**How to choose a probiotic?**

- **Genus, species, strain**
- **Expiration date**
- **Storage needs**
- **Dose** [a larger dose is not always better]
- **Formulation**
- **Evidence**

*ISAPP 2017*
Even if the best evidence is available, it does not automatically lead to improved health outcomes.

Evidence

<table>
<thead>
<tr>
<th>Aware</th>
<th>Accepted</th>
<th>Applicable</th>
<th>Able</th>
<th>Acted on</th>
<th>Agreed</th>
<th>Adhered to</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician</td>
<td>Patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Barriers extend from awareness to adherence

Adapted from Glasziou & Haynes. Evid Based Med. 2005;10:4-7
A final quote...
A final quote...

‘Make sure you have finished speaking before your audience has finished listening...’

Dorothy Sarnoff

Thank you for your attention
Deciphering a Probiotic Label

This is an example of a dietary supplement label for a product sold in the United States.

**Recommended Use:** Tells you what benefits you can expect from the product. Claims that relate the product to the structure or function of a healthy person’s body (such as “supports digestive health”) must be accompanied by a disclaimer that the FDA has not evaluated these claims.

**Dosage/Usage/Serving Size:** The amount that needs to be consumed to obtain the desired benefit.

**CFU (Colony Forming Units):** The number of viable bacteria in the product (sometimes designated as “live cultures”). Avoid products stating CFU “At time of manufacture.” Such labeling does not account for decline of CFU during storage. CFU listed is usually a total count, although count for each strain is preferred. CFU listed on the product label should equal the amount shown to be beneficial in human studies.

**Storage Information:** How to store the product to ensure product quality and safety.

**Use by/Expiration Date:** This tells you how long the probiotic will contain adequate levels of live probiotic to deliver claimed benefits. Probiotic bacteria are living microorganisms and their numbers can drop during storage. Products are formulated to have indicated CFU through the “use-by” date.

**Company Name and Contact Information:** Consumers can contact the company with questions, to get more information or to report any adverse effects.

**Genus, Species, and Strain of the Bacteria:** You need all 3 to know what probiotic you are getting. For the probiotic, Lactobacillus acidophilus MN 5, Lactobacillus is the genus, acidophilus is the species, and MN5 is the strain designation. A strain designation identifies the specific strain in the product. Strain specificity is important as different strains within the same species can have different health benefits. Choose products that identify the strains of bacteria contained in their product.

For more information visit ISAPPscience.org/probiotics or follow us on Twitter @ISAPPscience

---

Deciphering a Probiotic Label

This is an example of a hypothetical probiotic food supplement label for a product sold in Europe.

**Ingredients/Allergens:** This list contains all ingredients (active and inert) in descending order by weight. It is important to note if any allergens may be included in this list.

**Storage Information:** How to store the product to maintain probiotic potency.

**Use:** Take one capsule daily with a meal.

**Best before:** 13/12/2018
Lot number: 122456A3

**Company Name:** Probiotic Company
123 Probiotic Street
0111 Brussels, Belgium
www.probioticcompany.eu
info@probioticcompany.eu

For more information visit isappscience.org

---

Figure 2 How to read a label on a probiotic food supplement sold in the European Union. Copyright International Scientific Association for Probiotics and Prebiotics (2017) (https://isappscience.org/infographics). Published with permission.
Probiotic Checklist:
MAKING A SMART SELECTION
Not all products labelled “probiotic” are true probiotics

- It’s backed by science
Be prepared to hunt a little: there’s no single place to look for scientific evidence of probiotic health benefits. See www.ISAPPscience.org resources page for some guides.

- It provides an effective dose
When it comes to microorganisms, more are not necessarily better. The studies backing the product determine the ‘effective dose’. Most often, effective doses range from 100 million to 50 billion or more colony forming units (CFU)/dose.

- It provides the benefit I’m seeking
Different probiotic strains have different benefits—ranging from improving aspects of intestinal function to helping you fight off colds. Choose a product with evidence showing it can give you the health benefit you want.

- It’s safe for me
For healthy people, probiotics are generally safe to consume. Be sure to follow the instructions on the label. Pregnant women, infants, people with compromised immune systems, or people with short bowel syndrome should talk to a healthcare professional and the probiotic manufacturer before consuming.

- It’s labeled properly
For more details, see “Deciphering a Probiotic Label” at www.ISAPPscience.org/infographics/

- Names of the microbes
Look for the genus, species, and strain for every microbe in the product. This tells you what's in the product.

- CFU
This number tells you how many live microorganisms are in each serving or dose, all the way through to the expiration date (not “At time of manufacture”).

- Suggested dose or serving size
This tells you how much to take for the benefit.

- Proper storage conditions
Refrigeration may not be necessary.

- Company contact information
To get more information or report any problems related to the product.

A high-quality, effective probiotic does NOT have to be:
- Naturally found in the human gut (or ‘human-derived’)
- Able to colonize in the human gastrointestinal tract – most probiotics do not
- Coated to survive passage through the stomach (enteric coated)
- Composed of multiple strains

Check out ISAPP’s other infographics https://isappscience.org/infographics/or follow us on Twitter @ISAPPScience
© 2016, International Scientific Association for Probiotics and Prebiotics
Probiotics might not do anything for your gut microbiome — and could even be bad for it, studies find.
STUDIES FOUND PROBIOTICS: MAY INTERFERE WITH NATURAL GUT HEALTH

SOURCE: CELL

PROBIOTIC WARNING
STUDIES CAST DOUBT ON BENEFITS OF PROBIOTIC PRODUCTS
Are Probiotics Money Down the Toilet? Or Worse?

Jennifer Abbasi
Probiotics labelled 'quite useless'
Probiotics transiently colonize the human gut mucosa in highly individualized patterns.

Probiotics perturb rather than aid in microbiota recovery back to baseline after antibiotic treatment in humans.

Two gut microbiota studies questioned probiotic health benefits.
Comments

- No clinical endpoints in either study
- Methodological concerns
- Probiotic colonization not needed
2 RCTs published in NEJM

The efficacy of probiotics for treating acute gastroenteritis has been negated.
Potential harms may be underreported

A 2018 systematic review found that about a third of the 384 trials it evaluated did not report information on harm and only 2% adequately reported components.

Aim: To assess harms reporting in published reports of RCTs assessing probiotics, prebiotics, and synbiotics.


Results: Only 2% of trials adequately reported harms.

Conclusion: Harms reporting in published reports of RCTs assessing probiotics, prebiotics, and synbiotics often is lacking or inadequate. We cannot broadly conclude that these interventions are safe without reporting safety data.
Probiotics

- Bright future?
- Waste of money?
Probiotics

• An updated (2014) definition
  – Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host

Examples
  ▪ Lactobacilla
  ▪ Bifidobacteria
  ▪ S. boulardii

The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic

Colin Hill, Francisco Guarner, Gregor Reid, Glenn R. Gibson, Daniel J. Merenstein, Bruno Pot, Lorenzo Morelli, Roberto Berni Canani, Harry J. Flint, Seppo Salminen, Philip C. Calder and Mary Ellen Sanders
Indications for using probiotics in children

Many well-documented indications for the use of specific probiotics
How to choose a probiotic?

- **Genus, species, strain**
  - *Bifidobacterium longum* ABC
  - *Lactobacillus plantarum* AB2
  - *Lactobacillus rhamnosus* CD3
  - *Lactobacillus salivarius* EF6
  - *Bifidobacterium longum* ABC

- **Expiration date**
  - Use by 12/12/2018

- **Storage needs**
  - Keep dry to maintain potency

- **Dose**
  - Colony Forming Units (CFU’s)
    - 100,000,000

- **Formulation**

- **Evidence**
Probiotics?

Waste of money!
Probiotics

• Bright future?

• Waste of money?
‚The reports of my death have been greatly exaggerated.‘

Mark Twain
The reports of the end of probiotics have been greatly exaggerated...
Gut microbiota modifications

- Bright future?
- Waste of money?
Failed predictions

Cellular phones will absolutely not replace local wire systems.

Martin Cooper
Failed predictions

"There's no chance that the iPhone is going to get any significant market share. No chance."

Steve Ballmer, Former Microsoft CEO, 2007
Failed predictions

“THE BEATLES HAVE NO FUTURE IN SHOW BUSINESS.”

Decca Records executive after The Beatles auditioned for them
1962
Gut microbiota modifications

• Bright future?

• Waste of money?
Thank you for your attention.
A starting quote.

'The more I learn, the more I realize how much I don't know.'

Albert Einstein
Strategies for gut microbiota modulation

- Probiotics
- Prebiotics
- Synbiotics
- Postbiotics
- Antimicrobials
- Faecal or vaginal microbiota transfers
• Two Studies May Change View of Probiotics: One Size May Not Fit All
• Are Probiotics Safe? We Really Don't Know
• Probiotics No Better Than Placebo for Gastroenteritis

• the trial medication required refrigeration over the 5 days, thus it could have been exposed to temperature extremes in the home or during transport, which could have affected bacterial viability.