Shared responsibility for Industry, Regulators and Press: What to do to get the consumer correctly informed on probiotics?

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Declaration of interests

- Guest professor @ the Vrije Universiteit Brussel, Brussels, Belgium
- Director of Science @ Yakult Europe BV, Almere, The Netherlands
- President of the Pharmabiotic Research Institute (PRI), Narbonne, France
The presentation flow

Complexity of the probiotic field
Where health and disease come together
Regulation
Food versus pharma
Nutrition controversy
It is not exceptional in the nutrition field
Has it accelerated and spread because of social media?
The solution
The roles of
• Industry
• Regulators
• Governments
• Researchers
• Press
• Consumers

The complexity of probiotic research

The numbers
• Our gut microbiota contains $38 \times 10^{12}$ microorganisms; 200 species
• A typical probiotic administration is +/- $10^9$ microorganisms; one to a few species/strains
• We swallow $10^{10}$ microorganisms / day with our saliva

The persons
• Each of us has an individual microbiota composition
• Eating a different diet with different composition and quantity,
at different times of the day
• Each is prone to different and varying levels of physical and mental stress
• With different and varying health or disease status
• With different life styles

The products
• Single versus multispecies
• Different dose and viability
• Different administration modes
• Different matrix and preservation modes
• With or without prebiotic

C. A. Febinia, 2017
The complexity of probiotic trials

**The endpoint diversity**

- Making it the most “powerful medicine” ever (?), influencing our microbiology, digestion, metabolism, immune and endocrine systems, brain, mood, ...
- Through a wide variety of mechanisms, mostly working simultaneously...

**The confounding factors**

- Age, smoking, compliance, geography, season, drug use (AB), ...

**The health status of the subject**

- *Food related claims*, need to be shown in a “healthy population”: how to proof a health claim in an already healthy population? How to define “health” anyhow?
- *Medical claims* can cure or prevent disease
- Immediate effects or results later in life? (Ca-absorption and osteoporosis)

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Probiotics: where health and disease come together

Modified from: Green and van der Ouderaa, 2003.
Health and disease is not a matter of “either/or”, there is a continuum (Rijkers et al. 2010)

**NEED to MANAGE the EXPECTATIONS**

Consumers are increasingly more health conscious with respect to their food:
- elderly trying to grow older in a healthy, trouble-less way
- parents trying to raise their children in an optimal, healthy way and willing to pay for it
- teenagers that appreciate safe, transparently and sustainably grown food

They tend to compensate their ‘fast-food behavior’ or overweight with e.g. ‘light products’, or products enriched with probiotics, vitamins, anti-oxidants, polyphenols or omega 3, 6 ...  

Their expectations, however, may be unrealistic, leading to disappointment and negative messages on social media and in the press. Education is crucial here.

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**Probiotics used for (too?) many applications**

Possible distribution of mechanisms among probiotics. Some mechanisms might be widespread among commonly studied probiotic genera; others might be frequently observed among most strains of a probiotic species; others may be rare; and others might not be present among all strains of the same species.

Evidence is accumulating on a cross-section of probiotic strains that suggest some generalizations can be made beyond strain-specific effects.

Hill et al., 2014; nature reviews | Gastroenterology & Hepatology
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The role of the regulator

Functional food

PROBIOTICS

Functionality (health) claim
- high in ...
- source of...
- improves ...
- maintains ...

Drug (medication)

Medical (Curing or Risk reduction) claim
- prevents ...
- cures ...

The labyrinth of regulations relevant for probiotics
### Functional foods

**Definition**: Food that has physiological functions, including regulation of biochemistries, the nervous system, the immune system, and bodily defense beyond nutrient functions.


### Dietary supplements

**Definition**: These are intended to supplement the diet: containing one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents and also to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement.


### Drugs

**Definition**: An article intended for the cure, mitigation, treatment, diagnosis, or prevention of disease.


### Biological product

**Definition**: Product containing a virus, serum, or toxin applicable to the prevention, treatment, or cure of a disease.


### Medical food

**Definition**: Products intended for external use in the dietary management of a disease or condition for which distinctive nutritional requirements have been established by medical evaluation and is formulated to be administered under the supervision of a physician.


### Live biotherapeutic agent

**Definition**: A biological product that contains live organisms, such as bacteria and is applicable to the prevention, treatment, or cure of a disease or condition of human beings excluding a vaccine.


### Natural health products

**Definition**: It is defined as a substance, or a combination of substances, a homeopathic medicine, or a traditional medicine, that is intended to provide a pharmacological activity or other direct effect in:
- diagnosing, treating, mitigating or preventing a disease, disorder or abnormal physiological state or its symptoms in humans;
- restoring or collecting organic functions in humans, or
- modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

### Probiotics

The live micro-organisms which when administered in adequate amounts confer a health benefit on the host. FAO/WHO

### Japan

**Category:** Functional foods and nutraceuticals

**Definition as per country:** As per Japanese system, these products are in distinct category named as Food for Specified Health Use, with a specific regulatory approval process separate from food fortified with vitamins, minerals, and dietary supplement not carrying FOSHU claims.

**Regulatory body:** MHLW, FOSHU

### Europe

**Category:** Functional foods

**Definition:** A food that beneficially affects one or more target functions in the body beyond adequate nutritional effects in a way that is relevant to either an improved state of health and well-being or to the reduction of risk of disease.

**Regulatory body:** FUFOSE

### China

**Category:** Functional foods

**Definition:** Functional food is defined as a food that has special health functions or is able to supply vitamins or minerals and has the capability to regulate human body functions.

**Regulatory body:** SFDA

### Brazil

**Category:** Functional foods

**Definition:** Functional foods constitute items to which health ingredients are added due to which have specific physiological function and/or are enhanced with added ingredients not normally found in the product, providing health benefits beyond their nutritional value.

**Regulatory body:** ANVISA

### New Zealand and Australia

**Category:** Functional foods

**Definition:** Functional foods are products which are supposed to serve physiological roles beyond the provision of simple nutrient requirements.

**Regulatory body:** FSANZ

### USA

**Category:** Dietary supplements

**Definition:** Dietary supplements are intended to supplement the diet: containing one or more dietary ingredients (including vitamins: minerals: herbs or other botanicals: amino acids: and other substances) or their constituents and also to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement.

**Regulatory body:** DSHEA

### USA

**Category:** Drugs

**Definition:** Drug is an article intended for the cure, mitigation, treatment, diagnosis, or prevention of disease.

**Regulatory body:** FDA

### USA

**Category:** Medical food

**Definition:** Medical food are those products intended for external use in the dietary management of a disease or condition for which distinctive nutritional requirements have been established by medical evaluation and is formulated to be administered under the supervision of a physician.

**Regulatory body:** FDA

### USA

**Category:** Biological product

**Definition:** Live biotherapeutic agent is a biological product; (1) contains live organisms, such as bacteria; (2) is applicable to the prevention, treatment, or cure of a disease or condition of human beings and (3) is not a vaccine.

**Regulatory body:** FDA

### India

**Category:** Functional foods, drugs

**Definition:** Food that has physiological functions, including regulation of biorhythms, the nervous system, the immune system and bodily defense beyond nutrient functions.

**Regulatory body:** FSSA, PFA, FDA

### Malaysia

**Category:** Functional foods

**Definition:** Currently no official definition available for functional food products in Malaysia.

**Regulatory bodies:** FSQD, Drug Control Authority, NPCB and Committee for the Classification of Food-Drug Interface Products

### Canada

**Category:** Natural health products

**Definition:** It is defined as a substance, or a substances, a homeopathic medicine or a traditional medicine, that is intended to provide a pharmacological activity or other direct effect in: Diagnosing, treating, mitigating or preventing a disease, disorder or abnormal physiological state or its symptoms in humans; Restoring or collecting organic functions in humans, or Modifying organic functions in humans, such as modifying those functions in a manner that maintains or promotes health.

**Regulatory body:** Natural Health Products Directorate

### Consequences for producers and researchers

**Need to follow the regulator path for the research, determining**

- Clinical trials set up and endpoints
- Research targets and objectives (mechanisms)
- Number of dossiers to prepare
- Number of administrative tasks to explore and understand
- Number of languages to use (application & communication)
The FMT example

- No initial regulation, although ...
- application in humans was based on observations from animal experiments
- Post-use regulated in a number of countries (treated as Drug or as Human Tissue)
- Application list is expanding without too much regulatory problems (C. dif; Metab. Syndr., Obesity, IBD, ...)
- Like probiotics: Sometimes successful, sometimes not!!!
- Try this in the FOOD arena !!!

Why is nutrition so controversial?
The presentation flow

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Why is nutrition so controversial?

• Is it because of the relation to health?
  to the environment?

• Is it because of the social media’s hunger for new material?

• Or both?
Cultural meat might not be climate friendly, but how many people read the full story?

Pressure to secure publicity for new research is fierce, so it's easy to see why the press team at the University of Oxford fed up a paper published in the journal Frontiers in Sustainable Food Systems, like this: "Growing meat in the laboratory may not be better for the climate in the long run than meat from cattle." It sounds a lot better than cultured meat in most scenarios seems to be better for the climate than cattle. This is the received wisdom, after all, so puncture a hole in that and you have a story.

And true to form many outlets gobbled up the findings. The BBC went with: "Cultured lab meat may make climate change worse." The independent chose: "Lab grown meat could cause more environmental damage than the real thing, scientists warn." Most of the (widespread) coverage was in a similar vein.

However, as FoodNavigator's own coverage of the research reflected, the actual findings were a lot more nuanced than the headlines - and indeed a fair chunk of the content below them - suggested. This is nothing new, but it doesn't make it any less concerning.

Let's take a look at what the researchers did and what they found.

Agricultural greenhouse gas emissions are responsible for around a quarter of current global warming. Replacing conventional cattle farming with "sabitecture" - meat grown in the lab using cell culture has therefore been touted as a way to impact.
The frequency for probiotics is increasing...

September 2018

Niv Zmora, Gil Zilberman-Schapira, Jotham Suez, ... Zamiel Halpern, Eran Segal, Eran Elinav

**Cell**

**Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features**

Jotham Suez, Niv Zmora, Gil Zilberman-Schapira, ..., Zamiel Halpern, Eran Segal, Eran Elinav

**Cell**

**Post-Antibiotic Gut Mucosal Microbiome Reconstruction Is Impaired by Probiotics and Improved by Autologous FMT**

Scientists have long favored probiotics as a simple and effective way to boost digestive health. But new research suggests they might not be as effective as we once thought. Through a series of experiments looking inside the human gut, researchers show that many people’s digestive tracts prevent standard probiotics from successfully colonizing them. In the first study, 25 human volunteers underwent upper endoscopies and colonoscopies to sample their baseline microbiome in regions of the gut. After the antibiotics had cleared the way, the standard probiotics could easily colonize the gut of everyone in the second group, but to the team’s surprise, this probiotic colonization prevented the host’s normal microbiome and gut gene expression profile from returning to their normal state after being followed for another 2 months. The scientists discovered that the probiotics successfully colonized the first tract of some people called the “persisters,” while the gut microbiomes of “resisters” expelled them. Moreover, the persister and resister patterns would determine whether probiotics, in a given person, had any impact on the host. Zmora and colleagues, led by Elinav, Chief of Gastroenterology at the Tel Aviv Medical Center to measure gut colonization directly.

In the second study, 23 human volunteers underwent upper endoscopies and colonoscopies to sample their baseline microbiome in regions of the gut. All of these volunteers were then divided into two groups. The first group consumed generic probiotic strains, while the second was administered a placbo. Both groups then underwent a second round of upper endoscopies and colonoscopies to assess their internal response to the intervention. After they had recovered on their own, the researchers questioned whether patients should be taking probiotics to counter the effects of antibiotics, as they are often prescribed in order to impede the gut microbiota after it’s cleared by antibiotic treatment. To date, only 15 volunteers were given a course of antibiotics and then randomly assigned to one of three groups: the first, a 3-month washout group; the second, a placebo group; and the third, a course of antibiotics and placebo. The research publishes as two back-to-back papers on September 6 in the journal Cell.

**Surprisingly**, we saw that many healthy volunteers were actually resistant in that the probiotics couldn’t colonize their GI tracts. This suggests that probiotics should not be universally given as a “one-size-fits-all” supplement. Instead, they could be tailored to the needs of each individual.

"Although all of our probiotic-consuming volunteers showed probiotics in their stool, only some of them showed them in their gut, which is where they need to be," says lead author Elinav. "If some people resist and only some people permit them, the benefits of the standard probiotics we all take can’t be as universal as we once thought. These results highlight the role of the gut microbiome in driving very specific clinical differences between people.”

— Elinav

**Probiotics labelled ‘quite useless’**

By James Gallagher

Health and science correspondent, BBC News

It is widely assumed that probiotics are good for you. But a new study has revealed that they are far from a universal panacea. The research published in the journal *Cell* suggests that probiotics are not always effective, and that their benefits can vary significantly from person to person.

"Despite widespread use, there is little evidence to support claims that probiotics are universally beneficial," said lead author Dr Elinav. "Our study shows that some people are unable to colonize with probiotics, while others can. This highlights the need for personalized, targeted treatment approaches."
The frequency for probiotics is increasing...

**What is New Here?**

Although all of our probiotic-consuming volunteers showed probiotics in their stool up until some of them showed them in their gut, which is where they need to be, we saw that many healthy volunteers were actually resistant in that the probiotics couldn’t colonize their GI tracts. This suggests that probiotics should not be universally given as a ‘one-size-fits-all’ supplement. Instead, they could be tailored to the needs of each individual. Why all the fuzz? Many MDs world-wide will disagree! Adverse side effects of antibiotic use with probiotics might even bring IBS. So we simply deposit our poo before we go on ABs or probiotics to become coprophagic?

In contrast to the current dogma that probiotics are harmless and benefit everyone, these results reveal a new potential adverse side effect of probiotic use with antibiotics that might even bring long-term consequences. In contrast, replenishing the gut with one’s own microbes is a personalized treatment that led to a full reversal of the microbiome effects.

**Why all the fuzz?**

Contrary to the current dogma that probiotics are harmless and benefit everyone, these results reveal a new potential adverse side effect of probiotic use with antibiotics that might even bring long-term consequences. In contrast, replenishing the gut with one’s own microbes is a personalized treatment that led to a full reversal of the microbiome effects.

**What is New Here?**

Although all of our probiotic-consuming volunteers showed probiotics in their stool up until some of them showed them in their gut, which is where they need to be, … “If some people resist and only some people permit them, the benefits of the standard probiotics we all take can’t be as universal as we once thought.”

“The scientists discovered that the probiotics successfully colonized the GI tracts of some people, called the ‘persisters,’ while the gut microbiomes of ‘resisters’ expelled them. Moreover, the persister and resister patterns would determine whether probiotics, in a given person, could be prescribed to different individuals based on their baseline features. This opens the door to diagnostics that would take us from an empiric universal consumption of probiotics, which appears useless in many cases, to one that is tailored to the individual and can be prescribed to different individuals based on their baseline features.”

Segal adds, “This opens the door to diagnostics that would take us from an empiric universal consumption of probiotics, which appears useless in many cases, to one that is tailored to the individual and can be prescribed to different individuals based on their baseline features.”

**Many MDs world-wide will disagree!**

Adverse side effects of antibiotic use with probiotics might even bring IBS. So we simply deposit our poo before we go on ABs or probiotics to become coprophagic?

“Contrary to the current dogma that probiotics are harmless and benefit everyone, these results reveal a new potential adverse side effect of probiotic use with antibiotics that might even bring long-term consequences.”

**Original article:**

Lin Yang & Graham A. Colditz


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**... while probiotics may have potential economic benefits**

- 70% of the US population is overweight
- 38% of the US population is obese
- 10% of the US population is diabetic

**Original article:**

Lin Yang & Graham A. Colditz


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https://www.toledoblade.com/Food/2015/06/23/70-of-Americans-overweight-or-obese-study-finds.html
What if all the French ate probiotics?

King et al.:  
– 2.4 million fewer days with RTI  
– 291 000 fewer courses of antibiotics  
– 581 000 fewer days sick leave  

Hao et al.:  
– 6.6 million fewer days with RTI  
– 473 000 fewer courses of antibiotics  
– 1 453 000 fewer days sick leave

How does this compare?  

• Better than vitamin C (RR=0.97)  
• Similar as hand washing (OR=0.54)  
• Similar than neuramidase inhibitors (-0.7 days)  
• Worse than gloves, masks and gowns (OR=0.32)
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The solution

The roles of
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  • Regulators
  • Governments
  • Researchers
  • Press
  • Consumers

The role of the industry.

• Industry should keep investing in high quality research, develop new food products with increased nutritional and/or health promoting properties.
• They should be clear on the use of the products they bring on the market, whether as food, food supplement, medical food or drug, in order not to confuse the consumer.
• Quality criteria for e.g. probiotic products should always be met (safety, sufficient numbers at the end of the shelf-life, viability after the GIT passage, and functionality as demonstrated by clinical trials).
Industry initiatives

The IPA criteria used to define a “probiotic” encompass 4 requirements:

• 1) taxonomic characterized at the species level and identifiable at the strain level;
• 2) safe for the intended use;
• 3) the probiotic status must be scientifically documented by at least one supportive human clinical study, according to generally accepted scientific standards;
• 4) must be alive in the product and in a sufficient amount to achieve the desired effect up to the end of shelf-life and when consumed.

• The ISAPP has defined similar criteria and added the need for the deposit of the strain in an international culture collection. (https://isappscience.org/minimum-criteria-probiotics/)

• In December of 2017 IPA presented a proposal to Codex Alimentarius regarding the establishment of guidelines for probiotic foods. Codex Alimentarius accepted this proposal and requested that Argentina prepare draft guidelines. These will be considered in the 2019 session of the Codex Alimentarius Committee on Nutrition and Foods for Special Dietary Use.

The role of the Researcher.

• The researcher should use established technologies
• Remain independent as academic authority and report in an unbiased way
• The peer reviewing process is critical for any publication, but should also be unbiassed and transparent
• In this way results will be published in high level journals and match homologous research from e.g. the medical field
The role of the Researcher.

While the potential application fields are expanding, even exploding, the consumer is entitled to a realistic view and honest expectations on the potential of these applications.

While the (social) media share the major responsibility in this translation, the briefing of the media through press releases, tweets or other fast media should be balanced and unbiased.

The role of the Media.

• All media should communicate in a realistic, non-skewed and balanced way on new research.
• As the communication concerns health aspects, the consumer is definitely in need of scientifically correct and balanced information, referring both to benefits and risks, so he can weigh the new info with existing and established science.
• Bloggers should refrain from commenting in a field that is not in their expertise, especially when health issues are concerned.
• ‘Lack of time to verify’ cannot be an excuse to publish fake or unchecked news, especially when health issues are concerned.
• The use of logo’s or brand names should only be used if they are really concerned, both for bad and good news.
The role of the regulator.

• Regulators should define feasible criteria allowing recognition of the research efforts.

• The evaluation should be done in the spirit of the category concerned and not be more severe for foods than e.g. for pharmaceutical products or clinical practices (FMT example).

The role of the food regulator.

• The regulator should try to clarify and simplify the status of probiotic-based products by clearing all current ambiguities.

• Various regulatory agencies in different countries should preferably adhere to a single definition and limit the category descriptions for probiotics (Codex?).

• The regulator should define the appropriate level of evidence for determining a health benefit for probiotics and should put safety and functionality ahead of commercial interests.

• However, they should also be flexible to absorb new science and developments when proper scientific evidence is provided (FMT case).
The role of the Governments.

• Control of compliance for the true probiotics
• Policing the ‘cowboy’ products
• Assisting and insisting regulators for a fair regulation that
  - Protects the consumer
  - Stimulates industry to innovate in new products and applications

The role of the Consumer.

• Consumers are more demanding regarding the quality of their food, but they should remain realistic regarding the potential of dietary supplements or functional foods.

• They are rightly looking for optimal ways to get the nutrients and compounds that they need, preferably produced via a natural and sustainable approach.

• They should realize, however, that there is a cost involved in the development of these products and there can be limits to their requirements. Certain levels of processing and packaging may be necessary for safety or functionality reasons.

• They should be critical as to the information they receive through social media and they should consult multiple, reliable sources to obtain a balanced answer to their question.
Increased demand for qualitative and sustainable choices

Industry

Develop products with increased quality, safety and efficacy

Consumer

Needs to control and act when necessary (probiotic mattresses)

Government

Probiotic Application

Assuring quality, composition, safety and efficacy

Regulator

Needs to develop regulation that is feasible, transparent and adequate (probiotic aircleaners), based on good (clinical) science

Media

Report correctly, unbiased with purpose to inform consumer on all aspects, both negative and POSITIVE (now mainly ‘forgotten’ as maybe not attractive enough?)

Research

Fortunately we came a long way, but maybe there is still some road to travel...

Thank you for your attention.

https://archive.org/details/prolongationoflifemetciala

http://content.time.com/time/covers/0,16641,20101004,00.html
The solution?

Let your food be your medicine.
Your medicine your food.

Hippocrates’ wisdom from the past