Contradictory effect of probiotics and prebiotics on vaccines efficacy and immune system: Is there any solution for the inconsistency?

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**Abstract**

*Backgrounds* Adjuvants are principally used in vaccines formulation because many antigens alone cannot stimulate immune system. During two recent decades, probiotics due to their safety and immunomodulatory effects have been proposed as adjuvants and new strategy in vaccination. The present article was investigated the effects of probiotics and prebiotics on vaccines efficacy and was evaluated the current issues and challenges in the development of probiotics as adjuvants.

*Data Collection Method* For each subject, a review of electronic sources was carried out in the PubMed and Google Scholar using appropriate key words such as: probiotics, prebiotics, immune system, vaccines efficacy, human, animal models. Studies that showed any effect of probiotics and prebiotics on immune system and vaccines efficacy (regardless of positive or negative effect) were investigated in this paper.

*Results* Various studies on the beneficial effects of probiotics and prebiotics on vaccines efficacy have shown conflicting results and therefore use of probiotics as adjuvants have been faced with challenges. Review of methods and approaches to determine adjuvant capacity of probiotics and prebiotics in both animal models and human indicated that these researches were different in the following areas: probiotics strains, probiotics doses, number of administered probiotics, duration of probiotics administration, probiotics formulation, co-administration of prebiotics with probiotics, animal models, time of vaccines administration, route of vaccines administration, type of vaccines, valence of vaccines, age of volunteers, and design of experiments and trials. Considering all mentioned differences, it is entirely unexpected to obtain the same or similar results in different studies.

*Conclusions* In order to resolve the problem, a special attention to proper design of experiments and implementation of good clinical practice, manufacturing of definite probiotics and prebiotics formulation and prospective controlled-studies to reassess safety and immunomodulatory effects of probiotics and prebiotics is necessary.

**Key words:** probiotic; prebiotics; immune system; adjuvant activity; vaccine efficacy; animal models.
Introduction

The vaccine-preventable diseases are annually responsible for the deaths of more than a million children under 5 years and currently, vaccination is still the best method to prevent infectious diseases and losses arising from them (1). But, it should be considered that the immunogenic part of vaccines lonely has had low efficacy in creating the protection against infectious diseases and basically adjuvants are used in vaccines formulation in order to create and potentiate the immune response in the body (2).

Adjuvants are added to vaccines formulation to accelerate and enhance the immunogenicity of antigens, to reduce the amount of antigens and immunizations number, to induce a longer protection, shortening the immune response time and to increase antigen delivery to immune system. In a general view, adjuvants are classified into: i) mineral adjuvants (aluminum hydroxide, calcium phosphate), ii) bacterial derivatives (cholera toxin or non-toxic protein elements like muramyl dipeptide), iii) emulsions of oil in water and/or water in oil (saponins, Freund adjuvant, montanide and MF59) and iv) the immune system stimulants (cytokines). But adjuvants are not completely safe and lead to emerge side effects. Side effects to adjuvants can be classified as local or systemic reactions. Important local reactions include pain, swelling, inflammation, injection site necrosis, lymphadenopathy, granuloma formation, wound and sterile abscess. Nausea, fever, joints inflammation, allergic reactions, anaphylaxis, organ specific toxicity and autoimmune diseases are the most important systemic adverse reaction to adjutants (2).

Unfortunately, adjuvants with high potential properties in creating immune response also have more side effects and toxicity. On the other hand, their uses are accompanied by some limitations. For example, aluminum hydroxide induces Th1 immune responses while the adjuvant has a weak property in potentiating immunogenicity of polysaccharide antigens (3, 4). Therefore, researches to find new adjuvants have always been continued and during two recent decades, probiotics due to their safety and immunomodulatory effects are the centre of attention as adjuvants (1, 5). The present article was investigated the effects of probiotics on vaccines efficacy in both animals and human, and was evaluated the current issues and challenges in the development of probiotics as adjuvants.

Data collection method

In order to study the subject, a retrospective review of electronic sources was carried out in the PubMed and Google Scholar data bases using appropriate key word such as: probiotics, prebiotics, immune system, vaccines efficacy, vaccines efficiency, human, animal models, adjuvant effect, boost effect and potentiation properties. Studies that showed any effect of probiotics and prebiotics on immune system and vaccines efficacy (regardless of positive or negative effect) were investigated in this paper. In order to avoid losing related articles, studies characteristics such as: strains and doses of probiotics; route, duration and time of probiotics administration; design of experiments and type of vaccines were not considered for reviewing. With this viewpoint, 19 studies were obtained from the search results and were investigated for the subject.
Results

**Effect of probiotics and prebiotics on vaccines efficacy in animals**

Different researches have shown the positive effect of probiotics and prebiotics on vaccines efficacy in animals. For example, the effect of Lactobacillus culture on efficacy of anti-Newcastle vaccine in Hubbard and Hubbard broilers through increasing the production of antibody titer (the culture had negligible effect on Shaver and Shaver broilers antibody production) (6), stimulation of mucosal immunity and improvement of oral Salmonella vaccine efficacy with simultaneous consumption of fructo-oligosaccharide (FOS):inulin mix as a prebiotic in mouse (7), enhanced the humoral immune response of lambs to *Escherichia coli* K88ab and bovine herpes virus type 5 (BoHV-5) vaccines (8), protection against simian immunodeficiency virus (SIV) via the vaginal or oral/intragastric administration of *Lactobacillus Plantarum* and *Lactobacillus Rhamnosus* in the macaque model (9) and improvement of antibody responses to Newcastle disease virus and infectious bursal disease virus vaccination using PrimaLac® (a multi-strain probiotic containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Enterococcus faecium* and *Bifidobacterium bifidium*) in broiler chickens have been reported (10).

On the contrary, enhanced delayed-type hypersensitivity (DTH) responses following the use of galacto- and fructo-oligosaccharides (GOS/FOS) as a dietary supplement in a murine influenza vaccination model (11), no improvement in humoral or innate immunity and absence of adjuvant effect of *Bifidobacterium longum* PCB133 after vaccination against Newcastle disease virus in turkeys (12), lack of peripheral immune responses after daily consumption of Protexin® (consist of *Lactobacillus acidophilus*, *Lactobacillus delbrueckii* subsp. bulgaricus, *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Bifidobacterium bifidum*, *Enterococcus faecium* and *Streptococcus salivarius* subsp. thermophilus.) in layer hens (13) and no significant effect on antibody production against Newcastle disease virus after supplementation of diet with Bioplus 2B® (contains *Bacillus subtilis* and *Bacillus licheniformis*) in broilers (14) have been reported.

**Effect of probiotics and prebiotics on vaccines efficacy in human**

Similar to animal researches, different human studies have shown contradictory results and different effects of probiotics on vaccines efficacy. For example, the following cases can be mentioned.

The observed difference between *Lactobacillus GG* and *Lactococcus Lactis* on the efficacy of an attenuated *Salmonella typhi* Ty21a oral vaccine is noteworthy. *Lactococcus Lactis* has had a remarkable effect on increasing the complement receptor type three (CR3) receptor expression on neutrophils (that plays a crucial role in several immunological processes including leukocyte extravasations and phagocytosis) while *Lactobacillus GG* had led to a greater IgA production. These results indicate that probiotics have different immunoregulatory effects on human immune system.
Paineau et al. reported that some strains of the seven probiotics (*Bifidobacterium lactis*, *Lactobacillus acidophilus* (two different strains), *Lactobacillus plantarum*, *Lactobacillus paracasei* and *Lactobacillus salivarius*) induce faster production of serum immuneglobulin, especially IgA, following the oral administration of cholera vaccine and considered them as adjuvants (16). Improvement of live-attenuated influenza vaccine immunogenicity (protection rates against the H1N1 and B strains were suboptimal and the rate for the H3N2 strain was 84%) (17), higher production of Hib-specific IgG in infants after administration of *Lactobacillus GG*, *Lactobacillus rhamnosus* LC705, *Bifidobacterium breve* Bbi99 and *Propionibacterium freudenreichii* to mothers four weeks before delivery and to their infants together with galacto-oligosaccharides (as a prebiotic) followed by diphtheria, tetanus, whole cell pertussis and *Haemophilus influenzae* type b (Hib) vaccination (18), enhanced immunologic responses of an anti-influenza vaccine via an increase in Th1 response and the virus neutralizing specific immunoglobulin A (IgA) after consumption of *Lactobacillus fermentum* CECT5716 two weeks before and after vaccination (19) and enhanced specific IgG antibody responses in infants receiving monovalent doses of hepatitis B vaccine at 0, 1 month and a combined diphtheria, tetanus and acellular pertussis-hepatitis (DTPa–HepB) B vaccine at 6 months after supplementation with *Bifidobacterium longum* BL999 and *Lactobacillus rhamnosus* LPR (the probiotics had not any immunomodulatory effect with 3 monovalent doses of hepatitis B vaccine) (20) have been reported in the literature.

In contrast to the above references, no immunostimulatory effect of *Bifidobacterium breve* strain Yakult (BBG-01) after vaccination with oral cholera vaccine in children under 5 years of age (21), no benefit effect on immune responses to tetanus, *Haemophilus influenzae* type b (Hib) and pneumococcal conjugate (PCV7) vaccines in infants after maternal supplementation with *Lactobacillus rhamnosus* GG (LGG) (22), no difference in innate immunity between probiotic and placebo groups following daily administration of *Lactobacillus acidophilus* LAVRI-A1 in infants for the first six months of life after vaccination with parenteral tetanus vaccine (23) and no significant antibody levels in children 9 months to 10 years who have received DTP-Hib vaccine or a 23-valent anti-pneumococcal vaccine (according to their age) and supplemented with low-fat milk fermented by *Streptococcus thermophilus* and *Lactobacillus casei* (*Lactobacillus acidophilus*, oligofructose and inulin added after the fermentation process), have been also reported (24).

**Discussion**

Although, probiotics have been proposed as adjuvants and new strategy in vaccination (25), however the existing basic and clinical research on the beneficial effects of probiotics and prebiotics on vaccines efficacy shows contradictory results. Review of methods and approaches of the mentioned articles indicated that these articles were different in the following areas:
- Probiotics strains
- Probiotics doses
- Number of administered probiotics (single or combination use)
- Duration of probiotics administration
- Probiotics formulation (directly added to food/water or use of a registered trademark formula)
- Prebiotics use (with or without prebiotics in final formula)
- Animal models (in animal studies)
- Time of vaccines administration (before, simultaneous or after supplementation with probiotics)
- Route of vaccines administration
- Type of vaccines (different antigens need different immune responses)
- Valence of vaccines (monovalent or polyvalent vaccines)
- Age, accordingly, differences in type, intensity and duration of immune responses of volunteers (infants or adults in human studies)
- Design of experiments and trials

Considering all above differences, it is entirely unexpected to obtain the same or similar results in different studies. Also, the following important points should be noted:

1. Health benefits and immunomodulatory effects of probiotics are strain specific and efficacy or inefficacy of one strain cannot be extrapolated to another strain (26).

2. Principally, animal studies are the basis studies for human clinical trials, but caution should be applied for probiotics because successful use of probiotics in animal models does not necessarily mean that similar health benefits or immunomodulatory effects will obtain in human clinical trials. For example, significant higher mortality rate (more than two-fold) in patients receiving probiotics for treatment of severe acute pancreatitis has been reported. The harmful effects of the probiotics had not been observed in preclinical studies and the increased mortality rate was unexpected in human clinical trials (27, 28).
3. Probiotics are administered as live microorganisms and can act opportunistically in critically ill patients. Sepsis, fungemia and gastrointestinal tract ischemia following the consumption of probiotics especially in immunocompromised, postoperative and hospitalized patients, critically sick infants and patients in intensive care units have been reported (29).

4. Another problem is lack of national or international surveillance programs, assessment and reporting system in order to collect, analysis, interpretation and consequently prevents adverse events following immunization that occur after the co-administration of vaccines and probiotics as adjuvants (30). For example, the result of a meta-analysis showed that there are not enough evidences for adding probiotics to formula fed infants in order to reduce allergic diseases (such as asthma and urticaria) and further research is needed for routine use of probiotics as supplements in infants (31).

Conclusion

Because of health benefits of probiotics, globally market of probiotic products has grown each year (32). Although the results of some researches have indicated the positive effect of probiotics on the vaccines efficacy, but other studies found no correlation between the consumption of probiotics and increase in the efficacy of vaccines. Considering: a) complexity and diversity of immune responses, b) various genuses, species and strains of probiotics which demonstrate different biological activity and immunomodulatory effects and c) different immune system-probiotic interactions which tend to different clinical trial results, the following activities should be performed: (i) proper design of experiments and clinical trials, (ii) proper implementation of good clinical practice and follow up studies for assessment of adverse events following immunization in human studies, (iii) establishment of a globally probiotics and prebiotics safety database network by collaboration of clinical scientists, vaccinologists, nutrition scientists, regulatory authorities, related international organizations and associations of all countries in order to share and exchange of information and experiences about probiotics and prebiotic uses, their effects on health and especially on vaccines efficacy, and (iv) worldwide prospective studies to reassess safety, health benefits and immunomodulatory effects with definite formulation of probiotics and prebiotics at first in healthy neonates, children, adults and elderly people and in the next step under highly controlled conditions in both infectious and non-infectious diseases patients.
References


