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# Efficacy of a synbiotic supplementation in the prevention of common winter diseases in children: a randomized, double-blind, placebo-controlled pilot study

**Mario Cazzola, Nhân Pham-Thi, Jean-Charles Kerihuel, Henri Durand and Serge Bohbot**

***Abstract*:**
**Background and aims:** The purpose of this study was to investigate the efficacy of a synbiotic supplementation in reducing common winter diseases in children.
**Methods:** A randomized, double-blind, placebo-controlled, multicentre study was conducted in young school-age children (3–7 years old) during a winter period. Participants were otherwise healthy children who suffered from at least three episodes of ear, nose and throat (ENT), respiratory tract or gastrointestinal illness during the previous winter. They were supplemented daily with either a synbiotic preparation (*Lactobacillus helveticus R0052, Bifidobacterium infantis R0033, Bifidobacterium bifidum R0071*, and fructooligosaccharide) or a matched *placebo* for 3 months. Over this period, all emergent health episodes of any type were recorded by parents in a diary. They were checked by investigators at regular monthly visits. The main study outcome was the percentage of children free of any episode during study course.
**Results:** We randomized 135 children (mean age: $4.1 \pm 1.0$ years) to the synbiotic group ($n = 62$) or placebo ($n = 73$) group. At least one illness episode was reported in 32 children in the synbiotic group and 50 in the placebo group (51.6% *versus* 68.5%). This corresponded to a significant 25% relative risk reduction (95% CI 0.6–44.3%; $p = 0.045$). This difference was due to a decrease in the number of children who suffered from at least one ENT, respiratory tract or gastrointestinal disorder (50.0% with synbiotic group versus 67.1% with placebo; $p = 0.044$). At least one sickness school day loss was noted in 25.8% of children with the synbiotic as compared with 42.5% with placebo ($p = 0.043$). No treatment related side effects were detected in either group.
**Conclusions:** This study suggests that a 3-month supplementation with this synbiotic preparation can decrease the risk of occurrence of common infectious diseases in children and limits the risk of school day loss.

***Keywords*:** *Bifidobacterium*, *Lactobacillus*, prebiotics, probiotics, respiratory tract and gastrointestinal infections, synbiotic

## Introduction

Probiotics, as discussed primarily in the context of the maintenance of health, represent an expanding research area. They are defined as living microorganisms that, on ingestion in certain numbers, exert health benefits beyond inherent general nutrition [Goldin and Gorbach, 2008; FAO/WHO, 2002].

Lactic acid bacteria and bifidobacteria are increasingly being administered to infants with the intention of improving health and, in effect, probiotic therapies are entering the therapeutic mainstream of paediatric disease [Van Niel, 2005]. Long-term use of these agents among infants has been beneficial in autoimmune and allergic disorders, such as inflammatory bowel diseases [Schultz and Sartor, 2000] and atopic eczema [Boyle and Tang, 2006]. Their use is also associated with increased resistance to acute enteric and respiratory infections [Hatakka *et al.* 2001; Szajewska and Mrukowicz, 2001].

Correspondence to:
**Mario Cazzola**
Dipartimento di Medicina Interna, Università di Roma 'Tor Vergata', Via Montpellier 1 00133 Rome, Italy
**mario.cazzola@uniroma2.it**

**Nhân Pham-Thi**
Department of Pediatric Pneumology and Allergology, Necker Enfants Malades Hospital, Faculté René Descartes Paris V, Paris, France

**Jean-Charles Kerihuel**
Vertical Laboratories, Paris, France

**Henri Durand**
Institut Rosell-Lallemand, Blagnac, France

**Serge Bohbot**
URGO Laboratories, Clinical Research Development, Chenôve, France

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The impact of probiotics in preventing respiratory tract infections seems to be interesting and not restricted to children. Daily dietary probiotic supplementation for 6 months was a safe effective way to reduce fever, rhinorrhoea, and cough incidence and duration and antibiotic prescription incidence, as well as the number of missed school days attributable to illness, for children 3–5 years of age [Leyer *et al.* 2009]. In otherwise healthy adults, the intake of a probiotic reduced duration and severity but not the incidence of common cold episodes [de Vrese *et al.* 2006]. The supplementation for 3 weeks of a probiotic did not modify the incidence of winter infections (respiratory and gastrointestinal) in elderly people, but duration of all pathologies was significantly lower than in the control group [Turchet *et al.* 2003]. Oral administration of a probiotic delayed respiratory tract colonization/infection by *Pseudomonas aeruginosa* in intensive care unit patients [Forestier *et al.* 2008]. This finding might explain why administration of probiotics is associated with lower incidence of ventilator-associated pneumonia than control [Siempos *et al.* 2010].

The action of probiotics is not developed exclusively in the intestine. By modulating immunological parameters, influencing absorption and secretion in the intestinal mucosa, after bacterial translocation, or mediated by products from carbohydrate fermentation and other microbial metabolic performances, probiotic effects also affect other organic systems [de Vrese and Schrezenmeir, 2002]. It is likely that probiotics are effective because they exert their effects on numerous cell types involved in the innate and adaptive immune responses, such as epithelial cells, dendritic cells, monocytes/macrophages, B cells, T cells, including T cells with regulatory properties, and natural killer (NK) cells [Ng *et al.* 2009].

Unfortunately, it is now clear that significant differences exist between different probiotic bacterial species and strains. Considering that no two probiotics are exactly alike, we should not expect reproducible results from studies that employ different species or strains, variable formulations, and diverse dosing schedules [Minocha, 2009].

Moreover, the low viability and survival rates of probiotics remain a problem for their therapeutic use. Appropriate prebiotics and optimal combinations of probiotics and prebiotics (synbiotics) could allow significantly better efficiency to be obtained. A prebiotic is a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host well being and health [Roberfroid, 2007]. Today, only bifidogenic, nondigestible oligosaccharides (particularly inulin, its hydrolysis product oligofructose and (trans)galactooligosaccharides) fulfil all of the criteria for prebiotic classification [de Vrese and Schrezenmeir, 2008]. They are dietary fibres with a well-established positive impact on the intestinal microflora. Synbiotics aim to enhance the survival and activity of proven probiotics *in vivo* as well as stimulating indigenous bifidobacteria. A recent trial showed that a regular, long-term intake of various synbiotics may improve health by reducing the incidence and severity of respiratory diseases during the cold season [Pregliasco *et al.* 2008].

The purpose of this pilot study was to evaluate the possible efficacy in reducing common winter diseases of a 3-month daily supplementation with a novel three-strain synbiotic preparation during the winter period in children aged from 3–7 years.

## Methods

### *Synbiotic preparation and strain characterization*

The synbiotic, ProBioBaby® (batch no. R0175 16S HM009032, R0175 Tuf HM009033), was provided by Lallemand SAS, Blagnac, France. Each 1.5 g sachet contained $5 \times 10^9$ CFU (*Lactobacillus helveticus* R0052: *Bifidobacterium longum* subsp. *infantis* R0033: *Bifidobacterium bifidum* R0071; Institut Rosell inc, Canada) and 750 mg of short-chain fructooligosaccharide (Actilight®, Beghin meiji, France). The individual strains R0052, R0033 and R0071 are deposited in the Collection Nationale de Culture de Micro-organisms (CNCM) of Institut Pasteur (Paris, France) as I-1722, I-3424 and I-3425, respectively. The genetic identification of *L. helveticus* R0052 has been described previously [Naser *et al.* 2005]. The 16S rRNA and *tuf* genes of R0033 and R0071 were sequenced and deposited in GenBank under accession numbers GU936672, GU936673, GU936674 and GU936675, respectively.

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### *Clinical investigation*

This multicentre, double-blind and placebo-controlled trial was conducted in France during December 2006 through to March 2007. This study was performed according to current French and European regulations. Study protocol and parents' information notice were submitted for approval to the French Sud-Est IV Ethics Committee. The study was registered to the French notification institution (AFSSAPS). Written consent to participate of both parents was obtained and study procedures were explained to children able to understand such information.

### *Studied population*

Children aged from 3 to 7 years, following an educational program (either at nursery or primary school) and never regularly treated with a synbiotic supplementation were recruited by their general practitioner if they suffered from at least three respiratory or gastrointestinal episodes during the preceding winter period diagnosed by the physicians. They were seen during a routine surveillance visit. They had no particular medical history and no symptom of an infectious viral disease for at least 2 weeks before the inclusion in the study.

### *Study design*

Each child was randomized to either a daily synbiotic or placebo supplementation for 3 months. Allocated treatment for 1 month was provided. A diary was given to parents and they were instructed to note any occurring health problem during the study course (nature of the problem and major symptoms, duration of the episode, daily body temperature during the episode, given paracetamol, duration of days from school). During the study course, nonsteroidal anti-inflammatory and steroidal molecules were not allowed. Children were then examined by the investigator at 28, at 56 (±3 days) and at 84 days (final visit). The compliance to allocated treatment was evaluated by questioning parents and counting the number of returned sachets. The new 1-month treatment was then given. The parents' diary completeness was carefully checked. Before the evaluation period, 14 days of lead-in phase was conducted for both treatments.

### *Treatments*

These treatments were presented as similar sachets containing a white–brown lyophilized powder to be diluted in a glass of water or milk. After dilution, aspect and taste were identical for the two treatments. In both groups, a single sachet was given daily, preferably in the morning with breakfast. The synbiotic group was supplemented with Immunostim®/ProBioBaby® (URGO France/Institut Rosell Lallemand) composed of *Lactobacillus helveticus* R0052 (formerly classified as an *acidophilus* species), *Bifidobacterium infantis* R0033, *Bifidobacterium bifidum* R0071 and fructooligosaccharides (FOS). The composition of the preparation contained $3 \times 10^9$ CFU of the spray-dried probiotic bacteria, with 750 mg FOS. The number of viable probiotic bacteria declared for the product was guaranteed by long-term stability tests carried out by the supplier. The placebo sachets contained only common excipients (starch and vanilla flavour).

### *Study outcomes*

Main study outcome was the percentage of children who suffered from at least one health problem of any nature during the 3-month study course. Secondary outcomes were the percentages of children suffering from at least one episode characterized by an ear, nose and throat (ENT), respiratory tract or gastrointestinal symptom, the percentage of children with at least one febrile episode (body temperature $\geq 38.5^{\circ}$C), the number of reported health problems per included child and the percentage of children with at least one health problem including one or more day school loss. Intercurrent events and side effects were checked at each visit by questioning parents (open questions).

### *Statistical analysis*

Although this was a pilot study, the number of patients to be included was *a priori* determined. The expected mean (±SD) number of episodes per child was $4.0 \pm 1.5$ in the placebo group during the study course. To detect a 20% decrease of this rate with the synbiotic treatment, 115 patients per group (i.e. 230 in total) were required ($\alpha$ risk of 5% and 80% study power). Randomization was balanced per centre and per block of six.

Principal analysis of the main study outcome was performed according to the intention-to-treat (ITT) principle. All randomized children were included in this analysis whatever the duration of their participation and their compliance to the studied treatments. A secondary analysis was conducted on the per-protocol (PP)

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**Table 1.** Baseline characteristics.

| Baseline characteristics | Placebo group ($n=73$) | Synbiotic group ($n=62$) |
|---|---|---|
| Age (years) (mean ± SD) | 4.2 ± 1.1 | 4.1 ± 1.0 |
| Boys/Girls (*n*) | 39/34 | 33/29 |
| (%) | (53.4/46.6) | (53.2/46.8) |
| Nursery school children (*n* (%)) | 47 (64.4%) | 38 (61.3%) |
| School age children (*n* (%)) | 36 (35.7%) | 24 (38.7%) |

population defined as all randomized subjects who took their medication for at least 14 days (required impregnation period for the synbiotic according to manufacturer recommendations). The same principles applied to the main outcome analysis were followed for processing the secondary parameters.

To test differences in the percentage of children presenting or not with the event of concern, a $2 \times 2$ chi-squared test was used. Relative risk reductions (RRR) were calculated with their 95% confidence interval (CI). To compare mean number of events per randomized children, a nonparametric Mann–Whitney *U*-test was used. A *p*-value of $<0.05$ was considered as indicating a significant difference. SPSS™ 13.0 software was used for statistical analysis that was performed on a nondisclosed database (allocated treatments exclusively identified with no indication about their nature).

## Results

### *Baseline characteristics and patients disposal*

The study was scheduled to include only the 2006–2007 winter period. However, patient accrual was much lower than expected due to stringent inclusion/exclusion criteria and rather than expanding study duration to the next 2007–2008 winter period, the study sponsor decided to stop recruitment on March 2007. Owing to low accrual rate, many investigators did not complete their full block of allocated treatments explaining the final between-group unbalanced number of patients.

From December 2006 to March 2007, 135 children were eligible for inclusion and recruited by 18 general practitioners located in France. They were 63 girls and 72 boys ($R=0.53$). Mean (±SD) population age was 4.1 ± 1.1 years (median: 4.0 years; range: 2–7 years). Sixty two children were allocated to the synbiotic treatment and 73 to the placebo group. All were not febrile at inclusion and none were suffering from ENT, respiratory tract or gastrointestinal symptoms. The median follow-up duration was 98 days (range: 1–159 days) and was similar in both groups. Fifteen patients in the placebo group (20.5%) and 19 in the treated group (30.6%) prematurely stopped allocated treatment (Table 1). The main reasons were the occurrence of an intercurrent health problem or of a study nonrelated intercurrent event. Six children (three in each group) refused to continue to take allocated medication. Four patients (three and one in placebo group and synbiotic group, respectively) were lost to follow up. Owing to a too low patient accrual, study inclusion was stopped in March 2007 despite not reaching the expected number of randomized patients.

### *Health event occurrence during study course*

Out of the 135 included children, at least one health event was recorded in 82 subjects (Table 2). There were 50 out of 73 in the placebo group (68.5%; 95% CI: 57.1–78.0%) and 32 out of 62 in the treated group (51.6%; 95% CI: 39.4–63.6%). There was a significant difference between the two groups ($p=0.045$). The relative risk of observing an event in the treated group as compared with the placebo group is of 0.754 (95% CI: 0.557 to 0.994). This corresponds to a significant 25% RRR (95% CI: 0.6–44.3%; $p=0.045$).

A total of 126 patients (58 and 68 patients in the placebo and synbiotic groups, respectively) received either treatment for at least 14 days (per-protocol population). A health event occurred in half of the treated group (53.4%) and in a majority of the placebo group (72.1%) with a significant difference ($p=0.031$). The relative risk of infection was equal to 25.8% in the treated group (RRR: 25.8%; 95% CI: 2.7–45.1%).

A number of 151 health events were reported (57.6% in the placebo group and 42.4% in the

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**Table 2.** Study outcomes.

| Children with at least one episode | Placebo group ($n=73$) | Synbiotic group ($n=62$) | $p$-value |
|---|---|---|---|
| Any symptoms ($n$ (%)) | 50 (68.5%) | 32 (51.6%) | 0.045 |
| At least one ENT, respiratory or digestive symptoms ($n$ (%)) | 49 (67.1%) | 31 (50.0%) | 0.044 |
| At least one school day loss ($n$ (%)) | 31 (42.5%) | 16 (25.8%) | 0.043 |
| Nature of the event | Number of events | | Total in two groups $n$ (%) |
| ENT | 33 | 25 | 58 (38.4) |
| Respiratory | 29 | 20 | 49 (32.5) |
| Digestive | 13 | 11 | 24 (15.9) |
| Miscellaneous | 7 | 5 | 12 (7.9) |
| Not specified (at least with one target symptom) | 5 | 3 | 8 (5.3) |
| Total | 87 | 64 | 151 (100.0) |
| Number of event per included child (mean ± SD) | 1.2 ± 1.1 | 1.0 ± 1.3 | $p=0.144$ |

ENT, ear, nose and throat; SD, standard deviation.

synbiotic group) by 82 children with at least one event. A majority of these events (76.2%) concerned the respiratory tract and the ENT area and some problems (15.9%) were digestive. Miscellaneous episodes included isolated fever, dysuria, headache, asthmatic episode, eczema and leg pain. The number of events per included child was higher, but not significantly, in the placebo group (1.2 ± 1.0 *versus* 1.0 ± 1.3; $p=0.144$).

Fever (body temperature $\geq$38.5°C) was recorded by 51 patients among the 151 recorded events. At least one such event was noted in 30 children (41.1%) in the placebo group and in 21 (33.9%) in the synbiotic group ($p=0.388$).

Overall, 67.1% and 50.0% of the children in, respectively, the placebo and the synbiotic group suffered from at least one event including ENT or gastrointestinal symptoms and this result is also significant ($p=0.044$). There was a reduced number of sickness school day losses (at least one day of school lost because of a health event of any nature) in the synbiotic group (25.8%), which is less than in the placebo group (42.5%) with a significant difference ($p=0.043$).

### *Adverse events*

Investigators reported a total of 24 adverse events in 20 children (Table 3). None were serious events. Most of these events were expected ENT, respiratory tract or gastrointestinal problems. In two cases (abdominal pain in the placebo group and an otitis media in the synbiotic group) the intensity of the event was noted as severe. Two adverse events with digestive problems were considered by investigators as possibly related to the study medication in the placebo group and none in the synbiotic group. Owing to events, allocated treatment was temporally or definitively stopped in seven children (four and three in the placebo and synbiotic groups, respectively). The reasons for premature study arrest are shown in Table 4.

## Discussion

This pilot study, conducted in children aged 3–7 years with previous acute respiratory or gastrointestinal episodes during the winter period but otherwise healthy, documented that a 3-month supplementation with the specific synbiotic preparation used in the study decreased the risk of occurrence of common infectious diseases and limited the risk of school day loss. Moreover, the used synbiotic was well tolerated and no adverse events were correlated to its administration.

In our study, the principal outcome was the percentage of children who suffered from at least one health problem of whatever origin during study course. To the best of our knowledge, this broad criterion has not yet been used to evaluate the possible beneficial effect of this type of treatment. Almost all published placebo-controlled studies have focused on ENT, respiratory tract or diarrheic episodes and appreciate the reduction of the

**Table 3.** Adverse events reported by investigators.

| | Placebo group ($n=73$) | Synbiotic group ($n=62$) | Total ($n=135$) |
|---|---|---|---|
| Number of children with at least one adverse event *n* (%) | 9 (12.3%) | 11 (17.7%) | 20 (14.8%) |
| Nature of the adverse event | | | |
| Digestive problem | 5 | 1 | 6 |
| Varicella | 2 | 3 | 5 |
| Dysuria | 1 | 1 | 2 |
| Flu-like symptoms | 1 | 1 | 2 |
| Adenoidectomy | | 1 | 1 |
| Ankle oedema | | 1 | 1 |
| Ankle sprain | | 1 | 1 |
| Eczema | 1 | | 1 |
| Laryngitis | | 1 | 1 |
| Leg pain | | 1 | 1 |
| Otitis | | 1 | 1 |
| Throat ache | | 1 | 1 |
| Topical allergy (cream application) | | 1 | 1 |
| Total | 10 | 14 | 24 |

**Table 4.** Reasons for premature study discontinuation.

| Reason for study arrest | Placebo group | Synbiotic group | Total |
|---|---|---|---|
| Consent withdrawal | 2 | 1 | 3 |
| Intercurrent health event[a] | 4 | 4 | 8 |
| Nonmedical intercurrent event[b] | 1 | 4 | 5 |
| Nonauthorized treatment during study | 1 | 2 | 3 |
| Noninclusion criteria detected during study course | 0 | 1 | 1 |
| Protocol deviation (inappropriate dosing) | 1 | 3 | 4 |
| Refusal to take medication | 3 | 3 | 6 |
| Lost to follow up | 3 | 1 | 4 |
| Total | 15 | 19 | 34 |

[a]Varicella ($n=5$), digestive problem ($n=2$) and acute bronchitis ($n=1$).
[b]Hospitalization of the mother ($n=1$), death of the mother ($n=2$ children of the same family) and not specified ($n=2$).

number of these episodes over a given period as compared with controls. This approach requires a careful classification of episodes as well as a precise differentiation of successive events occurring with the same patients. This is usually difficult to process as for numerous acute events, especially in a paediatric population, many similar symptoms are often present. Furthermore, despite apparently symptom-free delay, it is frequently not certain that patient is suffering from clearly distinct events. In addition, an intercurrent health problem of different origin may mask an episode of concern. For these reasons, it was decided not to categorize episodes but to include all medical health events (except traumatic injuries). In the same way, it was decided not to count events but to use a more stringent parameter, the number of children free of any events during the study course. It was considered that this method was less prone to the introduction of possible interpretation bias. In addition a secondary analysis was conducted by selecting only children free of events including any target symptoms (i.e. ENT, respiratory tract or gastrointestinal symptoms) to verify that any decrease in percentage of event-free children can be related to the expected beneficial effect of the tested synbiotic. Finally, a very strict ITT strategy was used.

Under these conditions, compared with placebo, our study has detected a significant 25% RRR in the percentage of children who suffered from at least one health event during the

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treated winter period. This reduction was of the same magnitude when patients who were treated for at least 14 days are concerned. Furthermore, this effect is significantly related to a decrease in the rate of occurrence of events with ENT, respiratory tract or gastrointestinal symptoms. In the symbiotic group, episodes also appeared to be less severe as suggested by the significant reduction of the number of children who lost at least one day of school.

These results contrast with the results of a meta-analysis which documented that the incidence of respiratory tract infections does not appear to be considerably influenced by prophylactic administration of probiotics, although probiotics may have a beneficial role in reducing the severity and duration of subsequent respiratory tract infections [Vouloumanou *et al.* 2009]. Nonetheless, they are in agreement with the observations of a clinically useful effect of various synbiotics in preventing incidence and severity of common diseases during the cold season in young adults. In the study by Pregliasco and colleagues, three different evaluations of a synbiotic versus placebo were conducted during the winter period in healthy volunteers [Pregliasco *et al.* 2008]. In all study stages, significant improvement of bowel functions, and significant decrease in the total length of respiratory episodes and of cough as well as in cold and flu episodes were reported. In another study, feeding synbiotics to newborn infants was safe and seemed to increase resistance to respiratory infections during the first 2 years of life [Kukkonen *et al.* 2008].

The main study limitation is due to the fact that the planned number of children to be included was not reached due to patient selection difficulties, such as obtaining the written consent to participate from both parents. This finding was not really unexpected considering that a French survey documented that only 21% of the parents would accept the participation of their children in a clinical trial and 74% would refuse mainly because of the risk of side effects, unproven efficacy and disagreement in principle [Autret *et al.* 1993]. The under-enrolment can explain the unbalanced number of children between groups as full randomization blocks were not completed by investigators. This fact may have had the potential to introduce a study bias but, while this cannot be excluded definitively, the coherence of the results is not in favour of this hypothesis.

In any case, we must highlight that the present trial was a pilot study and, accordingly, it was an exploratory study limited in size and scope, although it was approached rigorously and with the same level of scrutiny as pivotal trials, including public registration. Pilot trials can be used to predict the feasibility and operational acceptability of a protocol design planned for a pivotal trial and can achieve this end with comparatively few patients [Loscalzo, 2009]. Thus, the results of a pilot trial can help to guide the effective use of limited (financial and nonfinancial) resources essential for a successfully performed pivotal trial [Loscalzo, 2009]. Two other advantages include their use in identifying unpredicted harm early in the course of drug development and assessing the utility of a surrogate end point in the pivotal trial, but they cannot provide definitive support for specific mechanistic or therapeutic claims [Loscalzo, 2009]. Having defined our trial as a pilot study, we recognize the preliminary nature of its results, but we also strongly believe that the information gained during this trial was deemed to be invaluable because it demonstrated the feasibility of a large pivotal study.

In conclusion, the present study suggests a clinically relevant beneficial effect of a 3-month daily synbiotic regimen in preventing usual acute infectious illnesses, without carrying risk, in a school-age population of 3–7 year olds. In view of the potential clinical and social impacts that a synbiotic treatment may have, a large confirmatory trial and additional *in vivo* studies to identify the immunologic mechanisms that produce these benefits should be recommended.

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## Conflict of interest statement

None declared.

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