



# Our

Probiotic Research

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## Foreword

There has certainly been an influx of probiotic products on the market over the last 5 – 10 years and with over 12,000 research articles on probiotics listed on PubMed, we undoubtedly seem to be in a gut era.

These probiotic products take on a range of forms from yoghurt drinks to oat based products and chocolate to dietary supplements presented in capsules, tablets, liquid or powder form. With all of these different variations it is hard to know which product to choose without knowing more in depth information about the product and the company behind it.

Probiotic trials now being published are of good quality and have convincing results with much of the work being done in digestive disorders, immune response and pathogen inhibition. However, there is other work that also looks promising in the field of (amongst others) cancer prevention, obesity and autism.

This booklet provides an insight into Probiotics International Ltd (manufacturers of Protexin healthcare products Bio-Kult & Lepicol) and an update on research carried out to date.

## About us

Probiotics International Ltd (Protexin) manufacture probiotic supplements which are sold in over 80 countries worldwide. Manufacturing is at our purpose built facility in Somerset, South West, UK. Quality is of paramount importance, with a dedicated quality department and accreditations including cGMP and ISO 9001:2008, you can be sure each product

is manufactured to the highest standard. All of our products are tested to ensure that they meet label claims using independent, UKAS accredited laboratories.

To ensure that we continue to produce innovative, research based products we work with leading researchers at universities and institutes to ensure that we are always at the forefront of research.

## Our Protexin Strains

Our Protexin probiotic species are included in the European Qualified Presumption of Safety (QPS) list. The QPS lists were compiled by the European Food Standards Agency (EFSA) to assess the compiled evidence and confirm the safety and nomenclature of the bacteria used.

Our probiotic strains have an original strain lodged at a leading UK culture collection bank known as the National Collection of Industrial, food & Marine Bacteria (NCIMB) to ensure there is no genetic shift. Here, the master cell bank, composed of freeze-dried ampoules, is stored between 2°C to 8°C. Strain purity is confirmed by the absence of bacteriological contamination. From the Master cell bank, the Working Cell Bank cryovials are prepared and stored at -80°C.

Strain	Culture Collection number
<i>Bacillus subtilis</i> PXN 21	NCIMB 30223
<i>Lactobacillus casei</i> PXN 37	NCIMB 30185
<i>Lactobacillus rhamnosus</i> PXN 54	NCIMB 30188
<i>Streptococcus thermophilus</i> PXN 66	NCIMB 30189
<i>Lactobacillus acidophilus</i> PXN 35	NCIMB 30184
<i>Bifidobacterium breve</i> PXN 25	NCIMB 30180
<i>Bifidobacterium longum</i> PXN 30	NCIMB 30182
<i>Lactobacillus bulgaricus</i> PXN 39	NCIMB 30186
<i>Bifidobacterium infantis</i> PXN 27	NCIMB 30181
<i>Bifidobacterium bifidum</i> PXN 23	NCIMB 30179
<i>Lactococcus lactis</i> subsp <i>lactis</i> PXN 63	NCIMB 30222
<i>Lactobacillus plantarum</i> PXN 47	NCIMB 30187
<i>Lactobacillus helveticus</i> PXN 45	NCIMB 30224
<i>Lactobacillus salivarius</i> PXN 57	NCIMB 30225
<i>Lactobacillus fermentum</i> PXN 44	NCIMB 30226

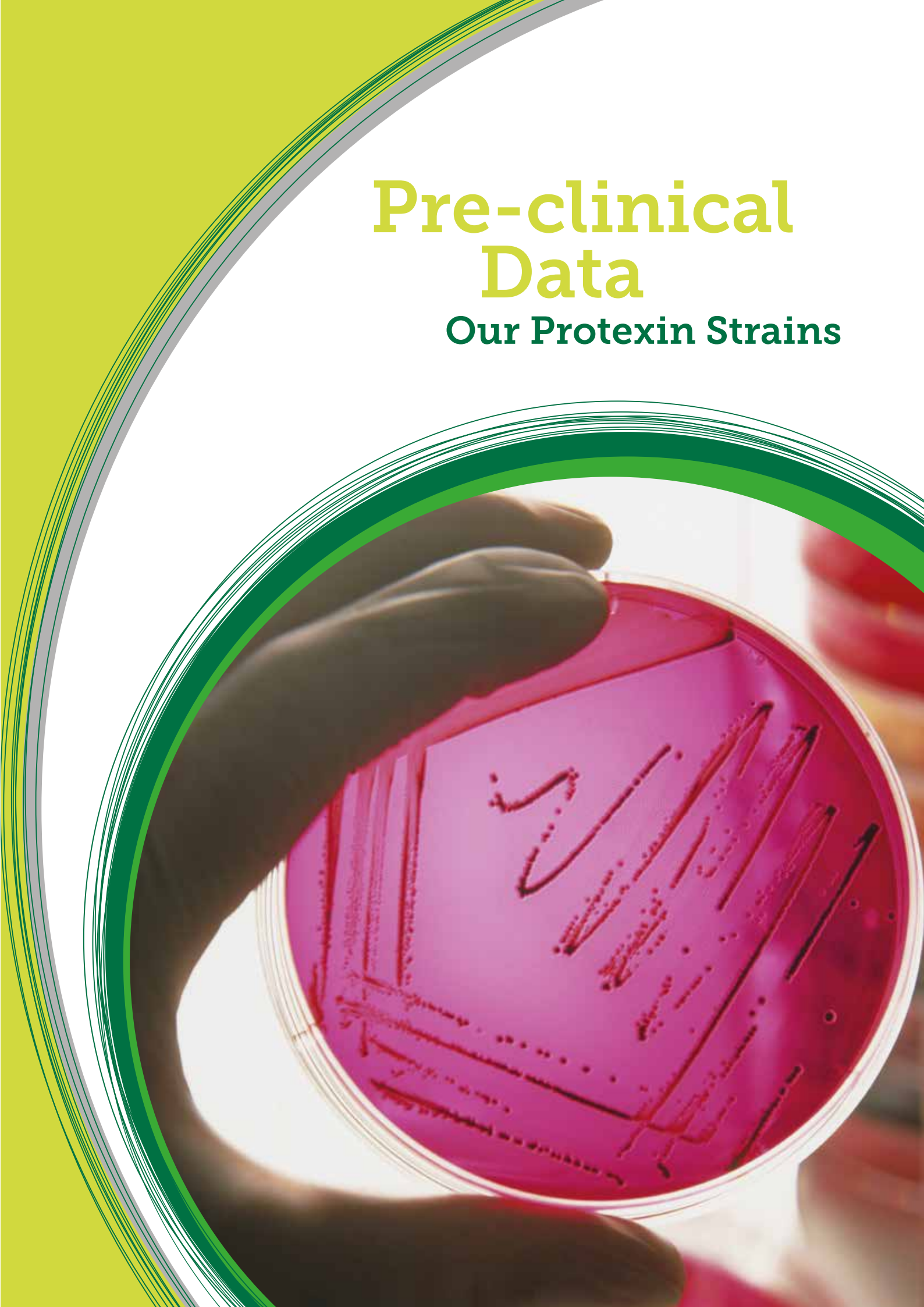
NCIMB – National Collection of Industrial, food & Marine Bacteria.





# Pre-clinical Data

**Our Protexin Strains**



# Antimicrobial Activity of Protexin Strains

## Objective

To assess the ability of Protexin probiotic strains to inhibit five common pathogens as well as haemolytic and hydrophobicity properties of these strains.

## Method

The inhibition activity was measured using agar spot method to ascertain the effect and well diffusion assays were used to look at the mechanism of action. The pathogen was spread onto agar plates and then the supernatant of a probiotic was pH neutralised with a buffer. If the supernatant had no effect then it would be assumed that acid is likely to be the cause of the inhibition.

Haemolytic activity was measured by using Columbia Agar with 5% Oxoid. Strains that produced green-hued zones around the spots of probiotics ( $\alpha$ -haemolysis) or did not produce any effect on the blood plates ( $\gamma$ -haemolysis) were considered non haemolytic. Strains displaying blood lysis zones around the spots were classified as haemolytic ( $\beta$ -haemolysis).

Hydrophobicity of the Protexin strains was evaluated by the microbial adhesion to hexadecane (MATH) assay. Strains adhering well to hydrocarbons were considered to be hydrophobic and strains adhering poorly were considered to be hydrophilic.

## Results

### Inhibition effect of Protexin strains on selected pathogens

	Pathogen strain													
	<i>S. typhimurium</i>			<i>S. aureus</i>			<i>E. coli</i>			<i>E. faecalis</i>			<i>C. difficile</i>	
	8h	24h	48h	8h	24h	48h	8h	24h	48h	8h	24h	48h	24h	48h
<i>L. acidophilus</i>	+++	+++	+++	+++	++	++	+++	++	++	+++	++	++	+++	+++
<i>L. rhamnosus</i>	+++	++	++	++	++	++	++	++	+	+++	+	++	++	++
<i>L. plantarum</i>	+++	+++	+++	+++	++	++	+++	++	++	+++	++	++	+++	++
<i>L. bulgaricus</i>	+++	++	++	++	++	+	+++	++	++	++	++	++	++	+
<i>L. casei</i>	+++	+++	+++	+++	++	++	+++	++	++	++	++	++	+++	++
<i>L. lactis</i>	+++	++	++	++	++	+	+++	++	++	++	+	+	++	+
<i>L. salivarius</i>	+++	+++	+++	+++	++	++	+++	+++	+++	+++	++	++	+++	+++
<i>L. fermentum</i>	+++	++	+	+++	+	-	+++	++	++	++	+	-	++	++
<i>L. helveticus</i>	+++	++	++	+++	++	++	+++	++	++	++	+	+	+++	++
<i>B. bifidum</i>	++	++	++	+++	++	++	++	++	++	++	++	++	-	-
<i>B. breve</i>	+++	++	++	++	+	+	++	++	++	++	+	+	+++	++
<i>B. infantis</i>	+	-	-	+	-	-	++	-	-	±	-	-	-	-
<i>B. longum</i>	++	++	++	++	++	++	++	++	++	++	++	++	-	-
<i>S. thermophilus</i>	++	±	±	++	±	±	++	±	±	++	-	-	-	-

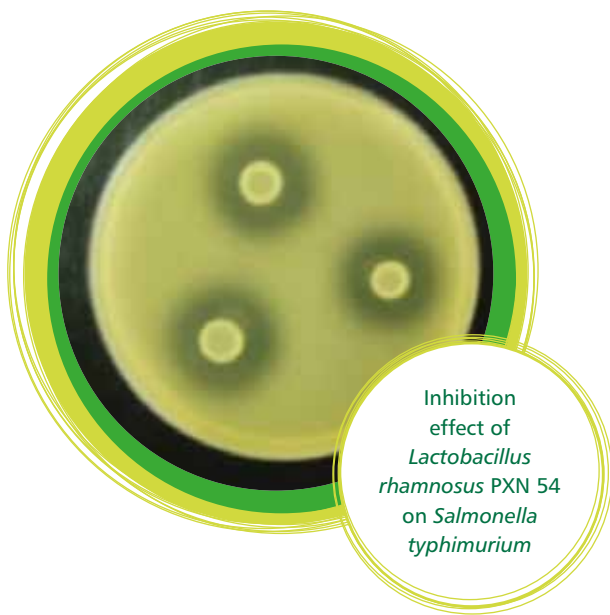
**Key:** (±) < 1 cm of inhibition but no clear halo  
 (-) no inhibition  
 (+) zone of inhibition between 0.5 – 1 cm

(++) zone of inhibition between 1.1 - 1.7 cm  
 (+++) zone of inhibition > 1.7 cm

## Protexin probiotics inhibit pathogens and have good cell adhesion properties

Antimicrobial activity was detected for all the Protexin strains. All nine lactobacilli showed good inhibition of the four pathogens: *Salmonella typhimurium*, *Staphylococcus aureus*, *Escheria coli* and *Enterococcus faecalis*.

The probiotic *B. breve* can be seen to be an effective inhibitor of the pathogenic strains tested. The other bifidobacteria appeared to be less effective than the lactobacilli species, however it could be that these species possess other probiotic effects (e.g. strengthening the epithelial barrier).



Well diffusion assays showed that there was more inhibition with non-adjusted pH than pH7 supernatant, suggesting that the most likely mechanism of action for the pathogen inhibition was acid production by the probiotic strains.

### Haemolytic activity of Protexin Strains

The data produced showed that none of the Protexin strains were found to be  $\beta$ -haemolytic. This is a positive result as haemolysis would not be a desired characteristic of probiotic strains as this is the splitting of red blood cells and the release of their contents into the blood plasma.

### Probiotic hydrophobicity

Strain hydrophobicity is an indicator of adherence to epithelial cells – hydrophobicity is considered as one of the main physical interactions during bacterial adhesion to cell linings.

Results have shown that all of the Protexin strains are hydrophobic, with *L. casei* PXN 37, *L. acidophilus* PXN 35, *L. salivarius* PXN 57, *L. rhamnosus* PXN 54, *L. fermentum* PXN 44, *L. lactis* PXN 63, *B. bifidum* PXN 23, *B. infantis* PXN 27, *S. thermophilus* PXN 66 and *B. subtilis* PXN 21 found to be highly hydrophobic.

## Conclusion

These findings show that there is significant antimicrobial activity of the strains tested and that a reduction in pH is responsible mainly for this activity (due to the production of acid from the probiotics). The results also show that the Protexin stains are not haemolytic and they have good cell adhesion properties.

# *In Vitro* Evaluation of Single and Multi-Strain Probiotics: Inter-Species Inhibition Between Probiotic Strains, and Inhibition of Pathogens

## Objective

To ascertain any ability of multi-species and multi-strain probiotics to inhibit each other and their ability to inhibit three pathogens – *Clostridium difficile*, *Escheria coli* and *Salmonella typhimurium*.

## Method

A cross-streak assay and agar spot test was used to evaluate the ability of 14 single-strains probiotics to inhibit each other. Pathogen inhibition was carried out using the agar spot test.

## Results

Inhibition was found for all species of probiotics. However, when single strains were tested against mixtures, the multi-strains preparations displayed significantly ( $p < 0.05$  or less) greater inhibition of pathogens in the majority of cases.

## Conclusion

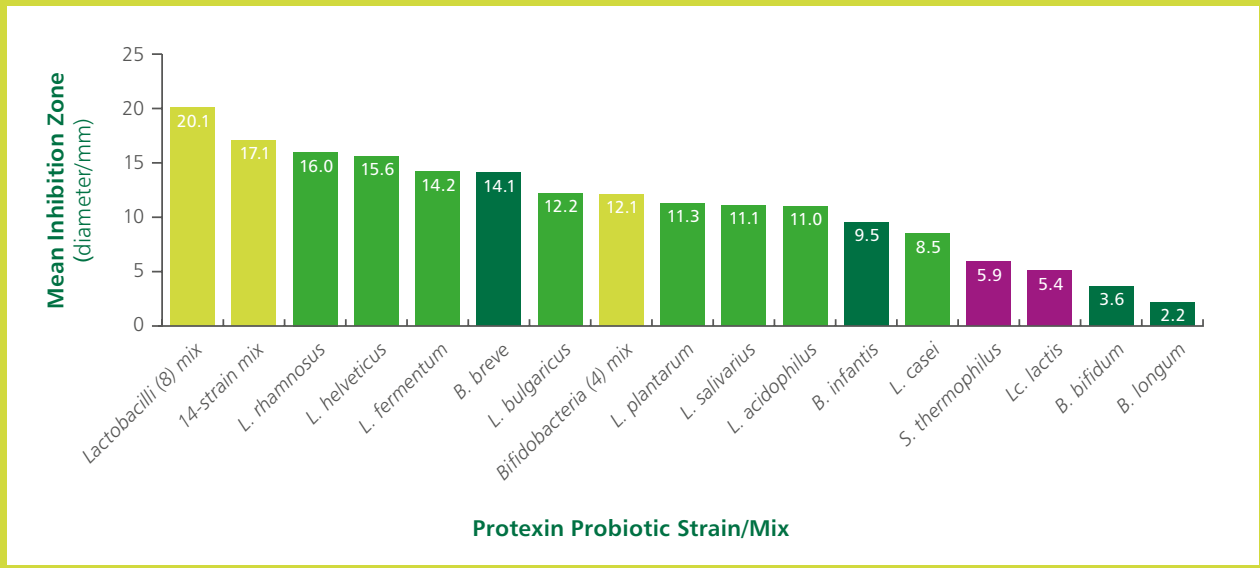
Despite concern that probiotic strains will inhibit each other when incubated together *in vitro*, in many cases a probiotic mixture was more effective at inhibiting pathogens than its component species when tested at equal concentrations of biomass. This suggests that using a probiotic mixture might be more effective than a single strain probiotic at reducing gastrointestinal infections.



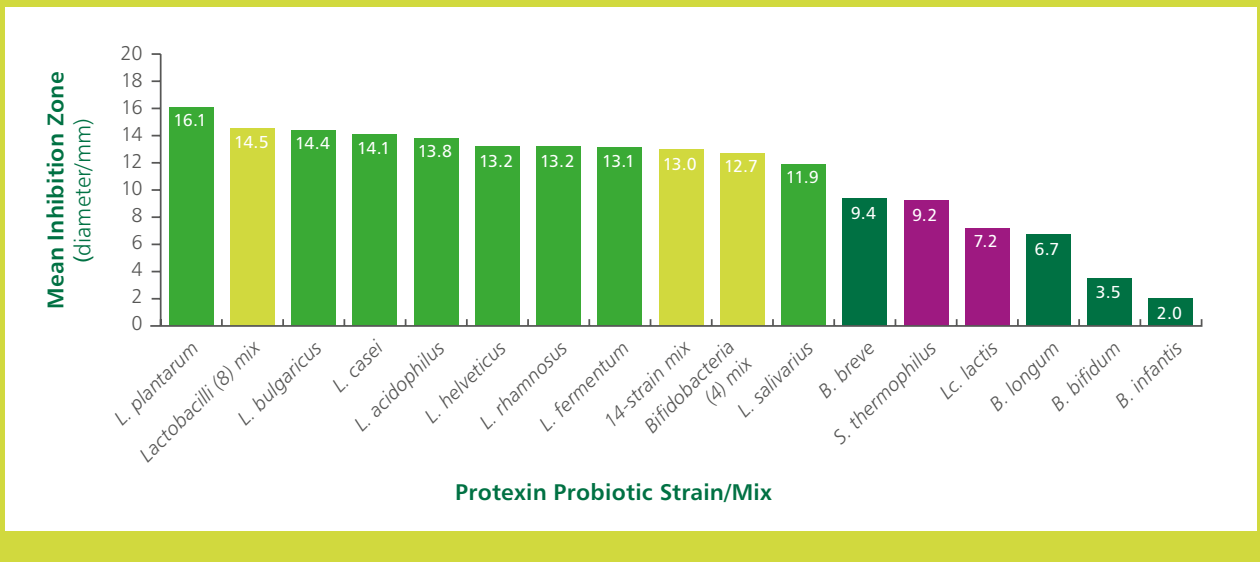
**Multi-Strain mixtures found to be more effective than single strains**



### Inhibition of *C. difficile* by Protexin probiotic strains and mixtures



### Inhibition of *E. coli* 1989 by Protexin probiotic strains and mixtures



# Evaluation of *Bacillus subtilis* Strains as Probiotics

## Objective

To evaluate spores of *B.subtilis* including commercial Protexin strain PXN 21 for their potential value as a probiotic and as potential food additives. This included resistance to gastric fluid, sporulation efficiency, formation of biofilms and effect on the immune system.

## Methods

Two isolates of *B.subtilis* examined were HU58 (human isolate) and PXN 21 against a laboratory strain – PY79. Sporulation was examined using the exhaustion method – inducing sporulation of all three strains and examining the spore counts. Biofilm formation was assessed looking at pellicle-like surface colonies on semi-solid media where different phases of colonisation could be assessed. Growth was assessed on MSgg medium, CM and CMK media.

Evaluation of the three spores through intestinal fluid was conducted in simulated gastric fluid (SGF) at pH 2, pH 3, and pH 4. Persistence of spores through the gastro-intestinal tract was measured following a single oral dose of each ( $1 \times 10^9$  CFU) to mice and examined faecal shedding.

Groups of inbred mice were also dosed orally ( $1 \times 10^9$  CFU) of PY79 or PXN 21 every 7 days for 10 weeks. At the end of the dosing regimen, splenocytes were cultured and stimulated with various exogenous antigens: *E.coli* LPS, CDTA of *C.difficile*, gluteraldehyde-inactivated *C.difficile* 630 spores, as well as two *C.difficile* spore coat proteins, CotC and CotD, and measurements of IFN- $\gamma$  were taken.

## Results

### Sporulation efficiency & mucin adhesion

PXN 21 showed the first detectable levels of heat resistant spores 2-3 hours post-induction and maximal counts at 8 hours. This closely resembled the human isolate HU58.

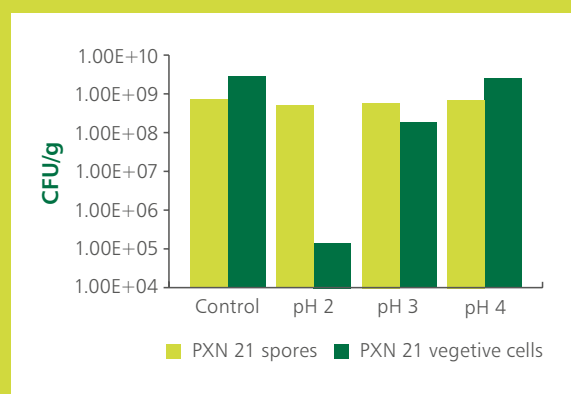
### Biofilm formation

The ability of PXN 21 to adhere to mucin was also assessed and compared against previously characterised strains using the mucin adhesion assay. PXN 21 demonstrated a significantly greater adhesion efficacy than the reference strains by more than 2 logs.

### Resistance to intestinal fluids

Spores exhibited almost no loss in viability after 1 hour of incubation. Vegetative cells were labile at pH 2 showing a 4-5 log reduction in CFU count after 1 hour incubation. However, at pH 4 (closely relating to the gastric pH after a full meal), vegetative cells showed no sensitivity to SGF and total viability was not affected.

### Survival of PXN 21 spores and vegetative cells in simulated gastric fluid for 1 hour



### Persistence of spores in the gastro-intestinal tract

Following a single dose of  $1 \times 10^9$  CFU, PXN 21 spores were still found to be present 18 days post dosing in the faeces of mice. This further suggests that PXN 21 is better adapted to gut residency than some other tested strains and this correlates with the ability of the strain to produce biofilms. The robustness of PXN 21 through intestinal fluids suggests that both vegetative cells and spores should pass through the stomach unscathed if they are consumed with a meal.

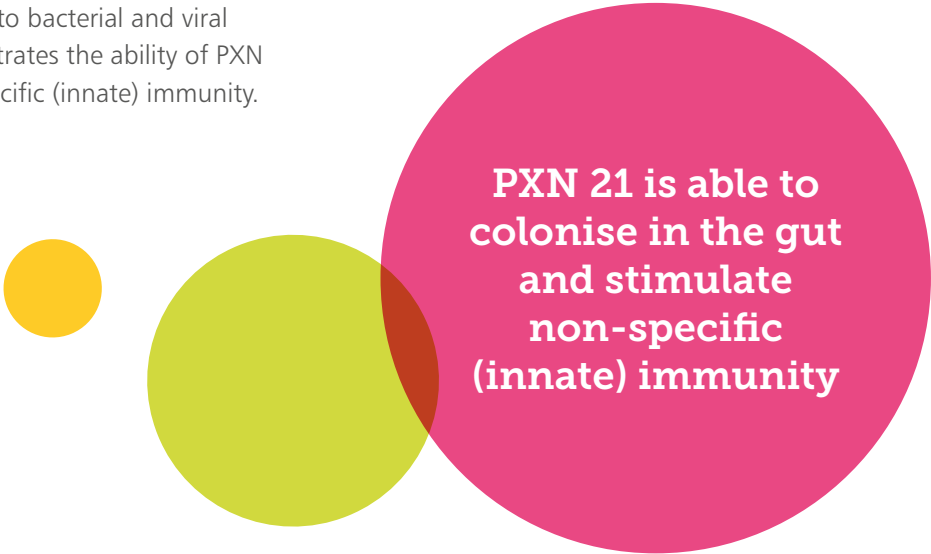
### Non-specific immune responses

PXN 21 immunised mice showed abundantly produced IFN- $\gamma$  when stimulated with a variety of antigens including *C.difficile* and *E.coli*. IFN- $\gamma$  is the primary cytokine involved in macrophage activation and mediating the host's defences to bacterial and viral pathogens. This result demonstrates the ability of PXN 21 spores to stimulate non-specific (innate) immunity.

## Conclusion

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PXN 21 is a fast sporulator and most closely resembles other natural isolates of *B.subtilis*. It is also able to adhere to mucin which is considered a beneficial feature to intestinal bacteria, enabling them to obtain nutrients and more efficiently colonise the mucosal epithelial layers. The ability of PXN 21 to create biofilms and persist in the GI tract demonstrates it's suitability to gut residency. This study also demonstrated the capability of PXN 21 to stimulate the immune system. All of this data supports the use of PXN 21 as a probiotic.



**PXN 21 is able to colonise in the gut and stimulate non-specific (innate) immunity**

# Use of *Bacillus subtilis* PXN 21 Spores for Suppression of *Clostridium difficile* Infection Symptoms in a Murine Model

## Objective

In this work, Protexin spores of *Bacillus subtilis* PXN 21, a bacterial species already widely associated with probiotic use, was used to suppress symptoms of *C. difficile* infection (CDI). The objective was to assess the potential capacity of this bacterium, as a probiotic, to protect against disease using a murine model of infection.

## Results

### Colonisation resistance

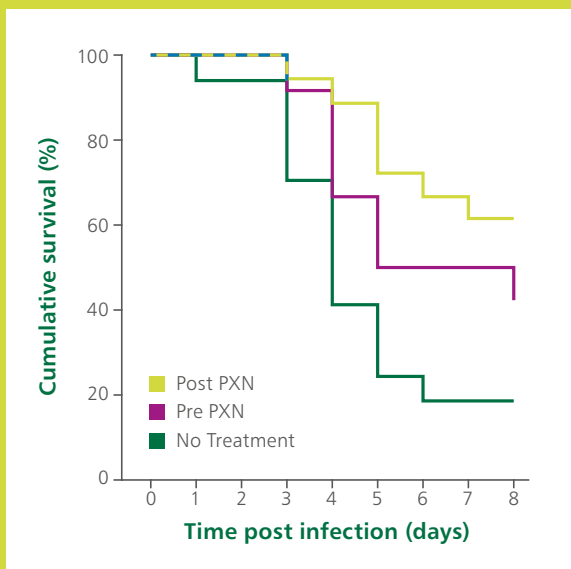
Levels of *C. difficile* spores present in faecal samples demonstrated that oral delivery of *B. subtilis* PXN 21 spores both prior to and post infection had no significant effect on reducing *C. difficile* colonisation.

### Attenuation of symptoms in a model of fatal disease

Delivery of PXN 21 spores prior to infection resulted in a survival rate of 41.6% while 66.6% survival was achieved in animals treated post-CDI; this compared to a survival rate of 16.6% in non-treated groups. Weight profiles of infected animals added further complexity to the results. Animals that survived infection having received probiotic treatment prior to infection displayed less weight loss than those infected with PXN 21 spores post infection.

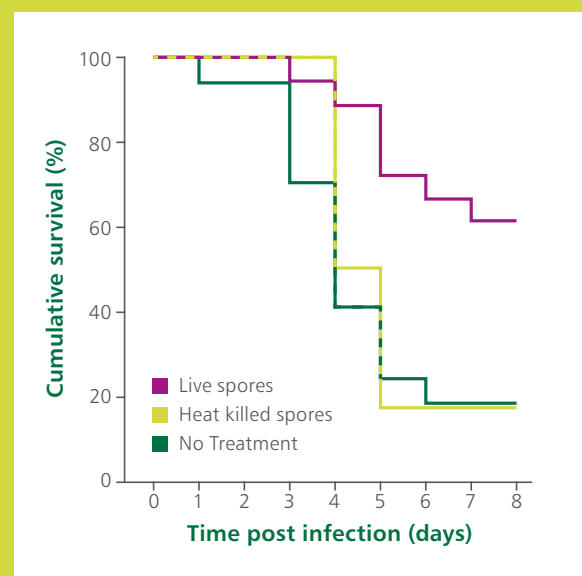
It was also shown that a dosing of mice post infection with killed spores showed almost no improvement on survival; by contrast, dosing with live spores markedly improved survival.

### Delivery of PXN 21 spores pre and post CDI



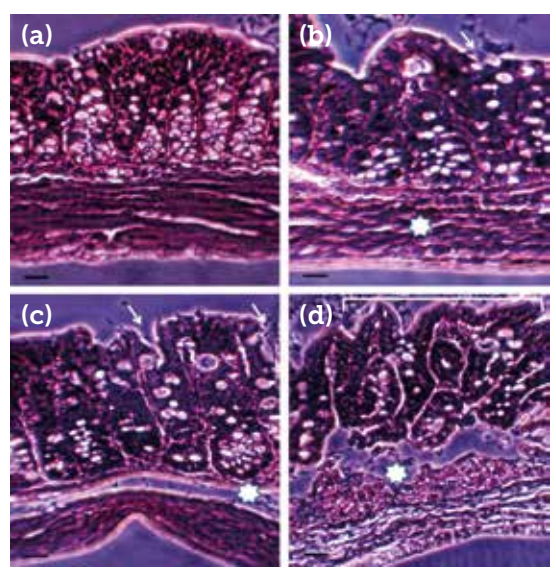
Pre PXN = Administration of *B. subtilis* PXN 21 prior to infection with *C. difficile*.  
Post PXN = Administration of *B. subtilis* PXN 21 after infection with *C. difficile*.

### Heat killed PXN 21 spores versus live PXN 21 spores against CDI'



## PXN 21 spores improved survival rates in a *C. difficile* infection model

### Histopathology



Haematoxylin and eosin (H&E) – stained sections of colon from *Clostridium difficile* VPI 10463 infected mice. (a) Uninfected mice, displaying healthy tissue and intact epithelial lining to colon; (b) mice treated with PXN 21 spores preinfection with some damage to epithelial structure but with lining still intact although evidence of mild oedema in the submucosa; (c) mice treated with PXN 21 spores post infection showed some damage to the integrity of the epithelial lining and some submucosal disruption; and (d) untreated mice displaying extensive damage to the colonic epithelial lining and erosion of the submucosa (shown by white arrows and stars). Scale bars 25 µm.

### Conclusion

This study demonstrates that live spores of *Bacillus subtilis* can attenuate the effects of *Clostridium difficile* infection in a murine model of disease by up to fourfold. The proposed mechanism of action is one through which the PXN 21 probiotic strain might stimulate the innate immune response. Suppression was not complete as animals were still infected but this work can form the basis for further studies to evaluate the effects of different doses of PXN 21 and ultimately the development of human clinical trials to assess the probiotic further.



# Antipathogenic Activity of Probiotics Against *Salmonella typhimurium* and *Clostridium difficile*: Is it Due to Synergies in Probiotic Mixtures or the Specificity of Single Strains?

## Objective

The aim of this *in vitro* study was to evaluate the influence of three single probiotics: *Lactobacillus casei* PXN 37, *Lactobacillus acidophilus* PXN 35, *Bifidobacterium breve* PXN 25 and a probiotic mixture containing the above strains plus twelve other strains belonging to the Lactobacillus, Bifidobacterium, Lactococcus, Streptococcus and Bacillus genera on the survival of *Salmonella typhimurium* and *Clostridium difficile*.

## Methods

The strains were evaluated using pH-controlled anaerobic batch cultures containing mixed faecal bacteria. Changes in relevant bacterial groups and effects of probiotic addition on survival of the two pathogens were assessed over 24 hours.

## Results

Quantitative analysis of bacterial populations revealed that there was a significant reduction in *S. typhimurium* and *C. difficile* numbers in the presence of probiotics compared with controls. Of the probiotic treatments, two single strains, namely *L. casei* PXN 37 and *B. breve* PXN 25, were the most potent in reducing the numbers of *S. typhimurium* and *C. difficile*. The probiotic mixture was equally as effective as the two most potent strains at reducing numbers of *S. typhimurium* and *C. difficile* as the two individual strains mentioned despite having fewer numbers of those specific probiotics by volume.

## Conclusion

These findings show that there is significant anti-microbial activity against *S. typhimurium* and *C. difficile* associated with Protexin strains, with PXN 25 & PXN 37 demonstrating particularly potent effects. These findings suggest that multi-strain mixtures can be as effective as those single strains alone. Taken in conjunction with other *in vitro* work this study can form part of the rationale for additional clinical trial work in infective and antibiotic associated diarrhoea (*C. difficile* is the most common pathogen associated with AAD).

Protexin strains demonstrated significant inhibition of *S. typhimurium* and *C. difficile*

# Human Clinical Trials

Our Protexin Strains



# The Effect of Probiotics on Faecal Calprotectin in Patients with Cystic Fibrosis

## Objective

This study was performed to assess the effects of a Protexin probiotic formulation on intestinal inflammation in a group of children with cystic fibrosis as measured by faecal calprotectin levels.

### The Protexin multi-strain formula

*Lactobacillus casei* PXN 37

*Lactobacillus rhamnosus* PXN 54

*Streptococcus thermophilus* PXN 66

*Bifidobacterium breve* PXN 25

*Lactobacillus acidophilus* PXN 35

*Bifidobacterium infantis* PXN 27

*Lactobacillus bulgaricus* PXN 39

Fructooligosaccharide (FOS)

Total viable count per sachet  $1 \times 10^9$  CFU

## Methods

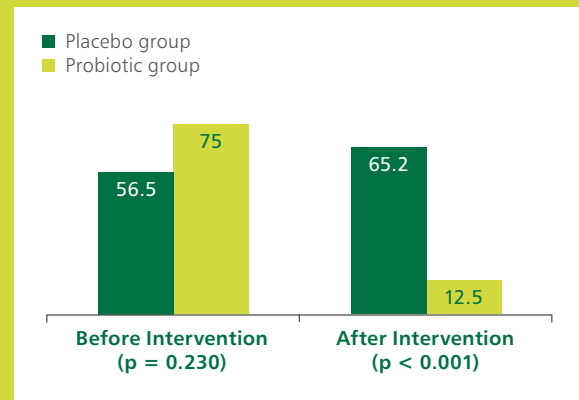
This was a double blind, randomised, placebo controlled trial in which 47 patients with cystic fibrosis were allocated to receive either a 7 strain probiotic formulation (24) or a placebo (23) for 4 weeks. Calprotectin levels were measured at baseline and after treatment to see if there was any effect. Patients were classified as having an abnormal or high calprotectin level if the value was above  $50\mu\text{g/g}$  of faeces.

## Results

31 of 47 enrolled patients (65.9%) were found to have abnormally high calprotectin levels; 13 in the placebo group and 18 in the probiotic group. This difference was not found to be statistically significant ( $p = 0.230$ ) so both groups were comparable at baseline. Following the intervention period a significantly lower proportion

of patients in the probiotic group were found to have high calprotectin levels than in the placebo group ( $p < 0.001$ ). The proportion of patients with high calprotectin levels actually increased in the placebo group.

### Percentage of patients with high Calprotectin Levels before and after treatment



## Conclusion

This study showed that about two-thirds of patients with CF had intestinal inflammation based on faecal calprotectin levels. Administration of the Protexin probiotic formulation was shown to decrease calprotectin concentrations and intestinal inflammation in CF patients. This study supports the rationale for further clinical trials looking at the use of probiotics to help manage abdominal symptoms associated with cystic fibrosis.

Protexin probiotics significantly decreased intestinal inflammation in children with Cystic Fibrosis

# Clinical and Immunological Effect of Probiotics in Childhood Atopic Dermatitis

## Objective

To study the clinical and immunologic effects of a Protexin probiotic formulation in infants and children with AD.

### The Protexin multi-strain formula

*Lactobacillus casei* PXN 37

*Lactobacillus rhamnosus* PXN 54

*Streptococcus thermophilus* PXN 66

*Bifidobacterium breve* PXN 25

*Lactobacillus acidophilus* PXN 35

*Bifidobacterium infantis* PXN 27

*Lactobacillus bulgaricus* PXN 39

Fructooligosaccharide (FOS)

Total viable count per sachet  $1 \times 10^9$  CFU

## Method

A randomised, double blind, placebo controlled study with 40 infants and children aged 3 months to 7 years with mild to severe AD. The infants and children received either the Protexin multi-strain probiotic or placebo for eight weeks. The Severity Scoring of Atopic Dermatitis (SCORAD) index was recorded at baseline and also at four and eight weeks. Allergic sensitisation was evaluated by measurement of total IgE at two points and skin prick test for common food allergens at baseline. IL-4 and IFN-gamma concentrations were measured from pre and post treatment blood samples.

## Results

Both groups received optimal skin care treatment for AD, but the Protexin group showed a significantly greater reduction in SCORAD than the placebo group between visits 1 & 2 and visits 1 & 3. However, the mean difference in IgE between the two groups was not statistically significant and no changes in cytokine profiles were detected.

## Conclusion

This study provides evidence that the a Protexin probiotic formulation clinically improves the severity of AD in young children. Further studies are needed to investigate the ability of probiotics to have a beneficial effect on the immune system.

Protexin probiotics significantly reduced symptoms of eczema in children

# The Clinical Efficacy of Multi-Strain Probiotics (Protexin) in the Management of Acute Gastroenteritis in Children Two Months to Two Years Old

## Objective

To determine the clinical efficacy of a Protexin probiotic formulation as adjunct treatment of acute gastroenteritis.

### The Protexin multi-strain formula

*Lactobacillus casei* PXN 37

*Lactobacillus rhamnosus* PXN 54

*Streptococcus thermophilus* PXN 66

*Bifidobacterium breve* PXN 25

*Lactobacillus acidophilus* PXN 35

*Bifidobacterium infantis* PXN 27

*Lactobacillus bulgaricus* PXN 39

Fructooligosaccharide (FOS)

Total viable count per sachet  $1 \times 10^9$  CFU

## Methods

51 children aged from 2 months to 2 years were included in this randomised, single blind clinical trial where they were assigned to either standard treatment group (control group) or standard treatment plus Protexin (Protexin probiotics group - one sachet). Frequency of diarrhoea, stool grade, length of hospital stay and any adverse reactions were reported.

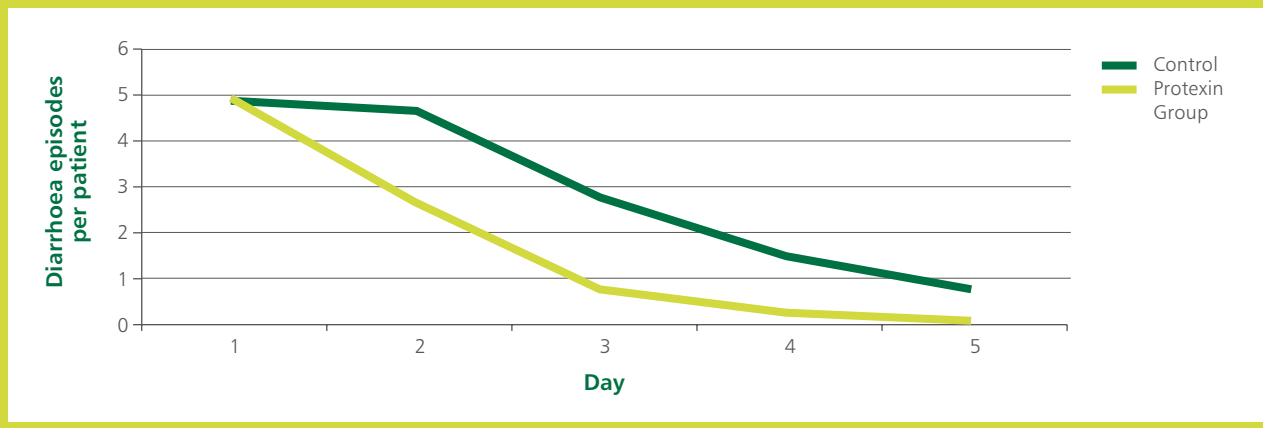
Standard treatment was used according to WHO guidelines; the use of oral rehydration solution, intravenous fluid if indicated, and zinc supplementation.

## Results

The probiotic group showed a decline in diarrhoea rate which was significant on the third day. Improvement in stool consistency was significant in the probiotic group on the second hospital day and the experimental group had a significantly shorter course of hospitalisation of at least one day when compared to the control group. No adverse reactions were reported from either group.



Mean frequency of diarrhoea in both study groups



## Conclusion

The Protexin probiotic formulation is both efficacious and safe in patients 2 months to 2 years old with acute gastroenteritis and should be considered as an additional therapeutic modality in the treatment of gastroenteritis.

Protexin probiotics significantly improved recovery in infants suffering with **Acute Diarrhoea**

# Synbiotic in the Management of Infantile Colic: A Randomised Controlled Trial

## Objective

To study the effects of a Protexin probiotic formulation in the management of infantile colic.

### The Protexin multi-strain formula

*Lactobacillus casei* PXN 37

*Lactobacillus rhamnosus* PXN 54

*Streptococcus thermophilus* PXN 66

*Lactobacillus acidophilus* PXN 35

*Bifidobacterium breve* PXN 25

*Lactobacillus bulgaricus* PXN 39

*Bifidobacterium infantis* PXN 27

Fructooligosaccharide (FOS)

Total viable count per sachet  $1 \times 10^9$  CFU

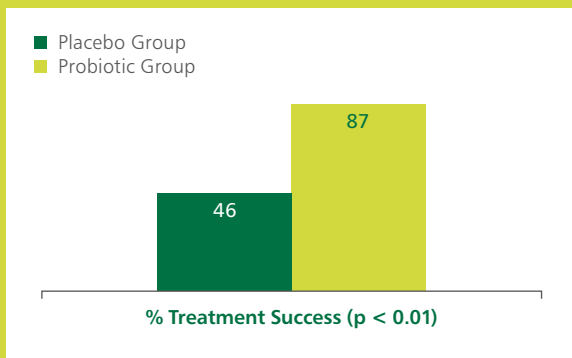
## Methods

This was a randomised, double blind, placebo controlled, prospective, parallel arm study in infants aged 2 weeks to 4 months diagnosed with infantile colic as defined by Wessel's criteria. The infants were randomly assigned to receive placebo or the probiotic mixture for 30 days. The primary objective was treatment success, defined as a reduction in average daily crying of at least 50% and the secondary objective was resolution of symptoms, defined as an average 90% reduction in daily crying. The primary and secondary endpoints were measured at 7 days after starting active treatment and at 30 days using symptom diaries completed by the parents.

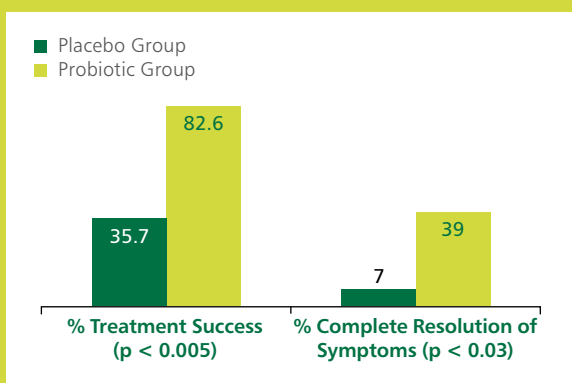
## Results

The two groups were comparable, with no difference seen in baseline characteristics. Treatment success was significantly higher in the probiotic group (82.6%) compared with the placebo group (35.7%), at day 7 ( $p < 0.005$ ). This difference was maintained at day 30 with a treatment success of 87% and 46% in the probiotic group and placebo group, respectively ( $p < 0.01$ ). In addition, symptom resolution was significantly higher in the probiotic group (39%) compared to the placebo group (7%) at day 7 ( $p < 0.03$ ). This significant difference was not maintained at day 30 (56% vs 36%,  $p = 0.24$ ). No adverse events were reported.

### Outcomes after 30 days of Treatment



### Outcomes after 7 days of Treatment



## Conclusion

This study provides evidence that the Protexin probiotic formulation used can help to manage symptoms of infantile colic without any reported side effects. The study supports the case for larger trials to see whether probiotics can prevent infant colic and also further trials to ascertain additional information such as optimal dosing or whether there is a dose dependent effect at all.

**Protexin  
probiotics  
significantly  
reduced  
infant colic**

# Probiotics for the Treatment of Pediatric *Helicobacter Pylori* Infection

## Objective

The aim of this study was to determine whether adding a Protexin probiotic formulation to standard *Helicobacter pylori* eradication therapy could minimize the gastrointestinal side-effect prevalence and improve the eradication rate.

### The Protexin multi-strain formula

*Lactobacillus casei* PXN 37

*Lactobacillus rhamnosus* PXN 54

*Streptococcus thermophilus* PXN 66

*Lactobacillus acidophilus* PXN 35

*Bifidobacterium breve* PXN 25

*Lactobacillus bulgaricus* PXN 39

*Bifidobacterium infantis* PXN 27

Fructooligosaccharide (FOS)

Total viable count per sachet  $1 \times 10^9$  CFU

## Methods

This was a double-blind, randomised, placebo controlled study conducted in 66 *H. pylori* positive children. They were all treated with the standard triple drug therapy protocol (omeprazole+amoxicillin+flurazolidone) and randomly allocated to receive either probiotic or placebo. All patients underwent oesophagogastroduodenoscopy. *H. pylori* infection was diagnosed by either rapid urease test (RUT) or histology. *H. pylori* status was assessed after completion of treatment. Side effects and adverse events were also recorded.

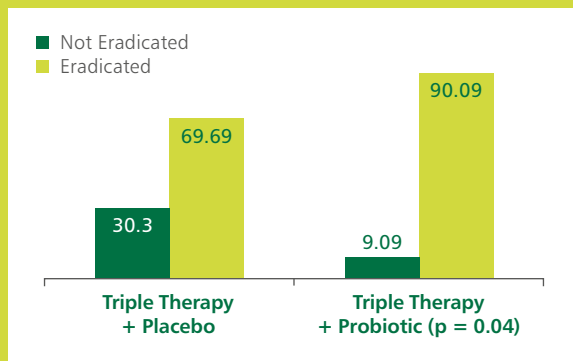
## Results

Both groups were comparable with no differences in baseline characteristics. All 66 patients completed the course of treatment and follow-up. The rate of *H. pylori* eradication was significantly higher in the probiotic group ( $P=0.04$ ). In the probiotic supplemented children there was a lower rate of nausea & vomiting ( $P=0.02$ ) and diarrhoea ( $P=0.039$ ) during treatment. No other serious adverse events were noted.

Protexin probiotics significantly reduced diarrhoea associated with antibiotics in children

# Protexin probiotics significantly increased *H. pylori* eradication rates in children

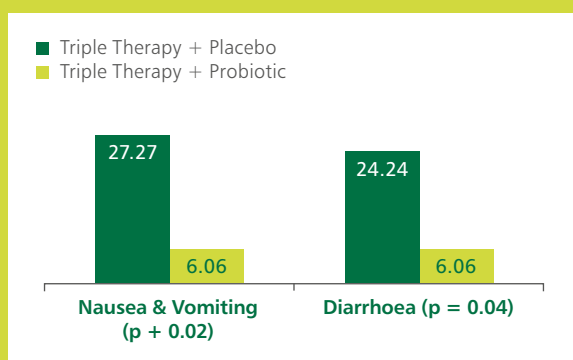
## Eradication of *H. Pylori* (%)



## Conclusion

This double blind, randomised, placebo controlled study demonstrates that the Protexin probiotic formulation used is potentially an excellent adjuvant therapy to help improve eradication of *H. Pylori* alongside conventional optimal treatment.

## Side Effect Rates (%)





# The Potential Use of Multi-Strain Probiotics as an Adjunct Treatment of Neonatal Pneumonia in a Tertiary Government Hospital: A Randomised, Controlled Clinical Study

## Objective

To determine the effect of a Protexin probiotic formulation as an adjunct in the treatment of neonatal pneumonia.

### The Protexin multi-strain formula

*Lactobacillus casei* PXN 37

*Lactobacillus rhamnosus* PXN 54

*Streptococcus thermophilus* PXN 66

*Bifidobacterium breve* PXN 25

*Lactobacillus acidophilus* PXN 35

*Bifidobacterium infantis* PXN 27

*Lactobacillus bulgaricus* PXN 39

Fructooligosaccharide (FOS)

Total viable count per sachet  $1 \times 10^9$  CFU

## Method

Thirty newborn babies were included in this randomised, controlled study. The inclusion criteria for the study was newborns 0 – 28 days old who were admitted to the neonate intensive care unit (NICU) diagnosed with pneumonia.

The babies were then randomised to two groups – group A (control group) received conventional treatment and IV antibiotics. Group B (treatment group) received conventional treatment, IV antibiotics plus one sachet of Protexin multi-strain probiotics per day.

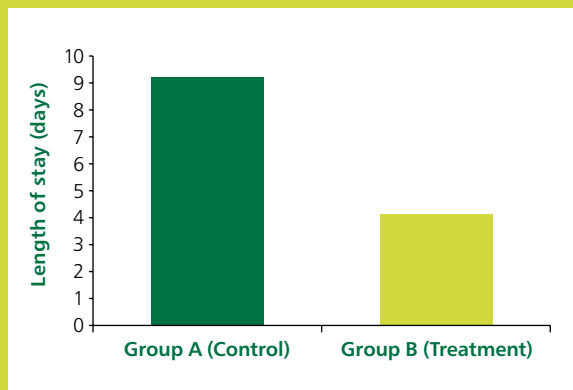
Symptoms of respiratory distress were measured such as rapid breathing and labored breathing as well as the length of hospital stay.

## Results

The results of this study showed a statistically significant difference in rapid breathing, with subjects in the group B (treatment group) having a shorter duration of rapid breathing ( $p < 0.001$ ). Differences were also seen with laboured breathing, early feeding tolerance (probably secondary to the shortened duration of respiratory distress) and length of hospital stay, with the experimental group showing significant reductions when compared to the control group. This also led to a significant reduction in neonatal sepsis in the experimental group (6.6%), compared to 66% in the control group.

Protexin probiotics significantly reduced sepsis and hospital stay in babies with **Neonatal Pneumonia**

Average length of hospital stay between both groups



## Conclusion

The supplementation of the Protexin probiotic formulation with IV antibiotics in patients admitted with neonatal pneumonia showed a significant difference in reducing the duration of symptoms of respiratory distress like rapid breathing and laboured breathing. Early feeding in neonatal pneumonia is one of the problems that is usually encountered in patients admitted either in the NICU or pediatric ward. This study showed that using the Protexin probiotic formulation as an adjunct to the treatment of neonatal pneumonia significantly reduces the length of symptoms associated with the condition and halves hospital stay.

# Role of Synbiotics in the Treatment of Childhood Constipation: A Double-Blind Randomised Placebo Controlled Trial

## Objective

To evaluate the effectiveness of a Protexin probiotic formulation on childhood constipation.

### The Protexin multi-strain formula

*Lactobacillus casei* PXN 37

*Lactobacillus rhamnosus* PXN 54

*Streptococcus thermophilus* PXN 66

*Bifidobacterium breve* PXN 25

*Lactobacillus acidophilus* PXN 35

*Bifidobacterium infantis* PXN 27

*Lactobacillus bulgaricus* PXN 39

Fructooligosaccharide (FOS)

Total viable count per sachet  $1 \times 10^9$  CFU

## Method

97 children aged between 4 and 12 years participated in this double-blind, randomised, placebo controlled trial. The children were allocated into 3 groups:

- A) 1.5ml/kg/day oral liquid paraffin plus placebo per day
- B) 1 sachet of Protexin probiotic per day
- C) 1.5ml/kg/day oral liquid paraffin plus 1 sachet of Protexin probiotic per day

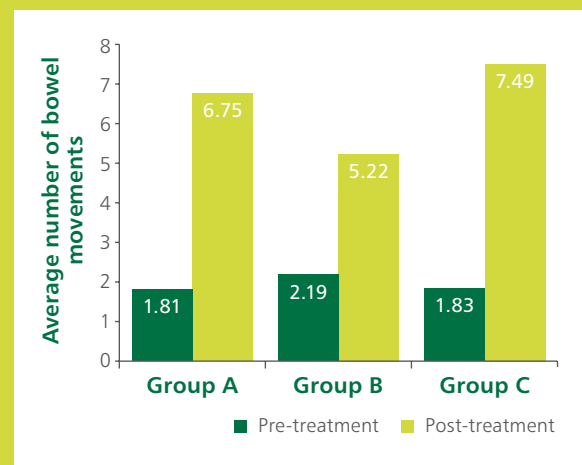
The groups were studied for 4 weeks with bowel movements (BMs), stool consistency, faecal incontinence, abdominal pain and painful defecation as the primary outcome. The secondary outcomes were incidence of adverse effects and success of treatment, which was determined as more than three BMs per week and less than two faecal incontinence episodes per month and no abdominal pain.

## Results

The results showed that there was a significant increase in the number of BMs per week in all study groups, but the highest rise ( $p = 0.03$ ) was in group C (liquid paraffin & probiotic group). Improvement in stool consistency and decrease in number of faecal incontinence episodes happened in all three groups without any statistical significance between all three.

There were no side effects reported in group B (probiotic only group) and this was significantly different to the other two groups which reported 18 side effects in group A and 21 in group C.

### Frequency of bowel movements per week before and after treatment



## Conclusion

This double-blind randomised placebo controlled trial showed that the Protexin probiotic formulation has positive effects on symptoms of childhood constipation without any side effects.

# The Effects of Probiotics on Childhood Constipation: A Randomised Controlled Double Blind Clinical Trial

## Objective

To study the effects of a Protexin probiotic formulation on symptoms associated with chronic constipation in children.

### The Protexin multi-strain formula

*Lactobacillus casei* PXN 37

*Lactobacillus rhamnosus* PXN 54

*Streptococcus thermophilus* PXN 66

*Lactobacillus acidophilus* PXN 35

*Bifidobacterium breve* PXN 25

*Lactobacillus bulgaricus* PXN 39

*Bifidobacterium infantis* PXN 27

Fructooligosaccharide (FOS)

Total viable count per sachet  $1 \times 10^9$  CFU

## Methods

This was a randomised, double blind, placebo controlled prospective parallel arm study in 56 children aged between 4 – 12 years diagnosed with chronic constipation as per Rome III criteria. Patients were randomly assigned to receive lactulose + probiotic or lactulose + placebo for a total of 4 weeks. The study assessed changes in stool frequency, consistency, abdominal pain and adverse events.

## Results

The two groups were comparable with no differences seen in baseline characteristics. After the intervention period, improvements were seen in both consistency and frequency of stool in both groups. However, the probiotic group had a significantly ( $p = 0.042$ ) greater increase in frequency of stool (2.08 bowel motions per week) compared to the placebo group (1.54 bowel motions per week). There was also a significantly better improvement in stool consistency within the probiotic group compared to placebo ( $p = 0.049$ ). Improvements were also seen in abdominal pain ( $p = 0.017$ ) and faecal incontinence ( $p = 0.03$ ) in the group taking the probiotic formulation. No side effects or adverse events were noted.

## Conclusion

This study provides evidence that the Protexin probiotic formulation used can help to improve stool frequency, stool consistency, abdominal pain and faecal incontinence in children with chronic constipation.

Protexin probiotics significantly reduced childhood constipation

# Synbiotics as an Adjunct to Treatment in Metabolic Syndrome

## Objective

The aim of this study was to evaluate the effects of a Protexin probiotic formulation alongside conventional lifestyle recommendations on insulin resistance and lipid profiles in individuals with the metabolic syndrome.

### The Protexin multi-strain formula

*Lactobacillus casei* PXN 37

*Lactobacillus rhamnosus* PXN 54

*Streptococcus thermophilus* PXN 66

*Bifidobacterium breve* PXN 25

*Lactobacillus acidophilus* PXN 35

*Bifidobacterium longum* PXN 30

*Lactobacillus bulgaricus* PXN 39

Fructooligosaccharide (FOS)

Total viable count per capsule  $1 \times 10^8$  CFU

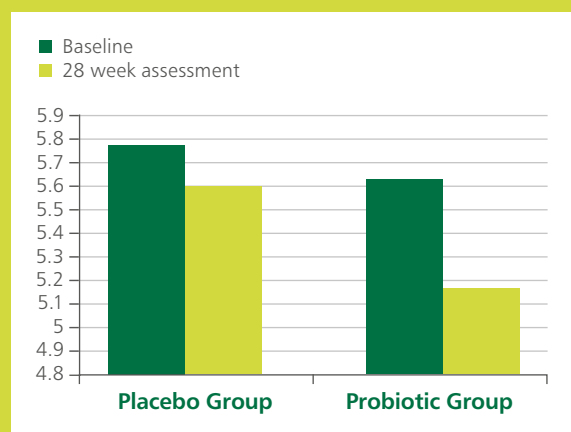
## Methods

The study was a prospective, randomised, double-blind, placebo-controlled clinical trial. Men and women aged 18 years and above with a diagnosis of the metabolic syndrome were randomised to receive either the probiotic preparation or placebo for 7 weeks alongside counselling to follow an energy-balanced diet and physical activity recommendations based on standardised clinical guidelines for the management of metabolic syndrome. Multiple anthropomorphic and biochemical parameters were assessed at baseline and at 7 weekly intervals for a total of 28 weeks.

## Results

38 patients were enrolled into the study and randomised into two groups of 19. Baseline characteristics were comparable with no difference seen in any of the measured parameters. Both groups showed improvements in said parameters but the probiotic group showed greater improvements and this was maintained through to the 28 week assessment suggesting that the probiotic formula had long lasting beneficial effects.

### Changes in Fasting Blood Sugar ( $p < 0.001$ )



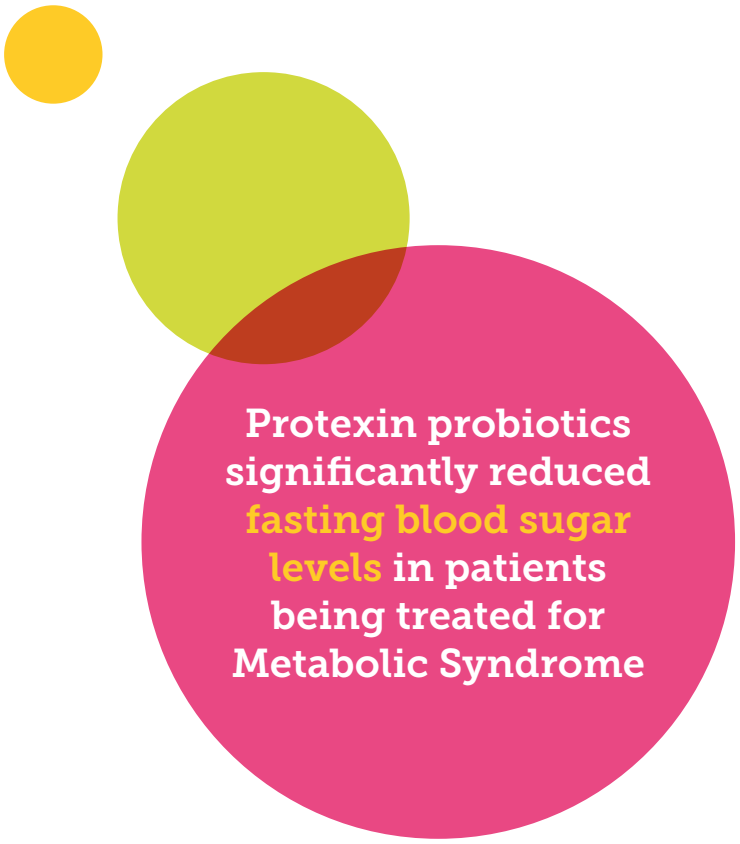
**Figure 1.** Changes in fasting blood sugar between the two groups. At baseline the difference between the two groups was not significant ( $p=0.731$ ) but, whilst both groups demonstrated improvements, there was a significant difference between the two ( $p < 0.001$ ) after treatment.

Statistically significant differences were also seen after 28 weeks in triglyceride ( $p < 0.001$ ), HDL ( $p < 0.001$ ) and total cholesterol levels ( $p=0.010$ ). Significant improvements were also seen in the insulin resistance (HOMA-IR) index and quantitative insulin sensitivity check index (QUICKI) during and after treatment.

## Conclusion

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This randomised, double-blind, placebo controlled study has found some evidence that probiotic supplementation augments the effects of lifestyle modification in the treatment of metabolic syndrome at least partially through the attenuation of insulin resistance and serum lipid levels. Further, larger and long term studies to evaluate clinical outcomes and quality of life measures are warranted to assess the long term use of probiotics as an adjunct to treatment in metabolic syndrome.



**Protexin probiotics significantly reduced fasting blood sugar levels in patients being treated for Metabolic Syndrome**

# Use of Synbiotics as an Adjunct in the Treatment of Non-alcoholic Fatty Liver Disease

## Objective

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world. Oral administration of synbiotics has been proposed as an effective treatment of NAFLD because of its modulating effect on the gut flora, which can influence the gut-liver axis. This study was designed to evaluate the effects of supplementation with a Protexin probiotic formulation on hepatic fibrosis, liver enzymes, and inflammatory markers in patients with NAFLD.

### The Protexin multi-strain formula

*Lactobacillus casei* PXN 37

*Lactobacillus rhamnosus* PXN 54

*Streptococcus thermophilus* PXN 66

*Bifidobacterium breve* PXN 25

*Lactobacillus acidophilus* PXN 35

*Bifidobacterium longum* PXN 30

*Lactobacillus bulgaricus* PXN 39

Fructooligosaccharide (FOS)

Total viable count per capsule  $1 \times 10^8$  CFU

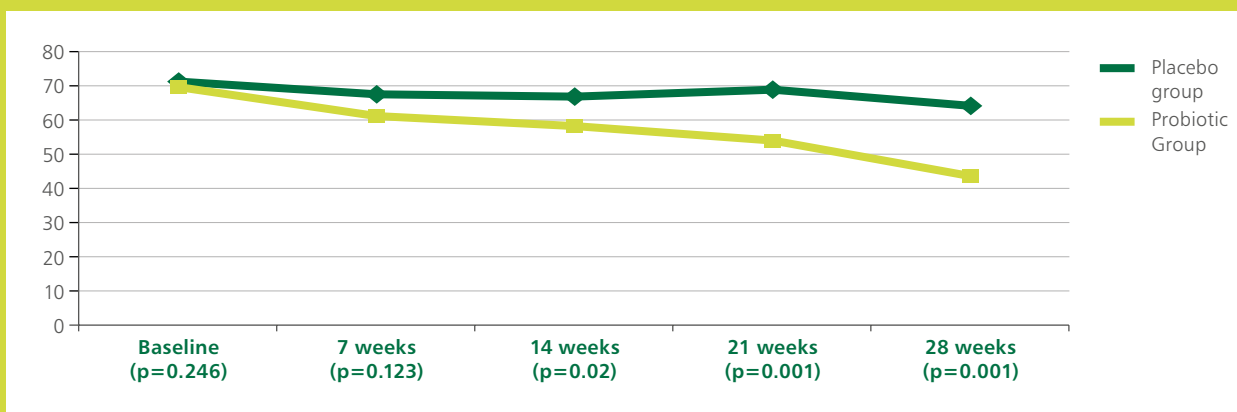
## Methods

This was a randomised, double-blind, placebo-controlled clinical trial conducted as a pilot study in adult patients with NAFLD who were supplemented twice daily for 28 weeks with either the probiotic or a placebo capsule. Both groups were advised to follow an energy-balanced diet and physical activity recommendations according to standardised clinical guidelines. Multiple anthropomorphic and biochemical parameters were assessed at baseline and at seven-weekly intervals for a total of 28 weeks. The primary outcome was determined as improvement in hepatic function based on reduction of hepatic enzymes.

## Results

Fifty two patients were enrolled into this study and randomised into the two groups. Baseline characteristics were comparable with no significant differences found between the two groups. Both groups showed improvements in alanine transaminase (ALT) as would be expected given the lifestyle changes implemented ( $p < 0.001$ ). However, the mean reduction

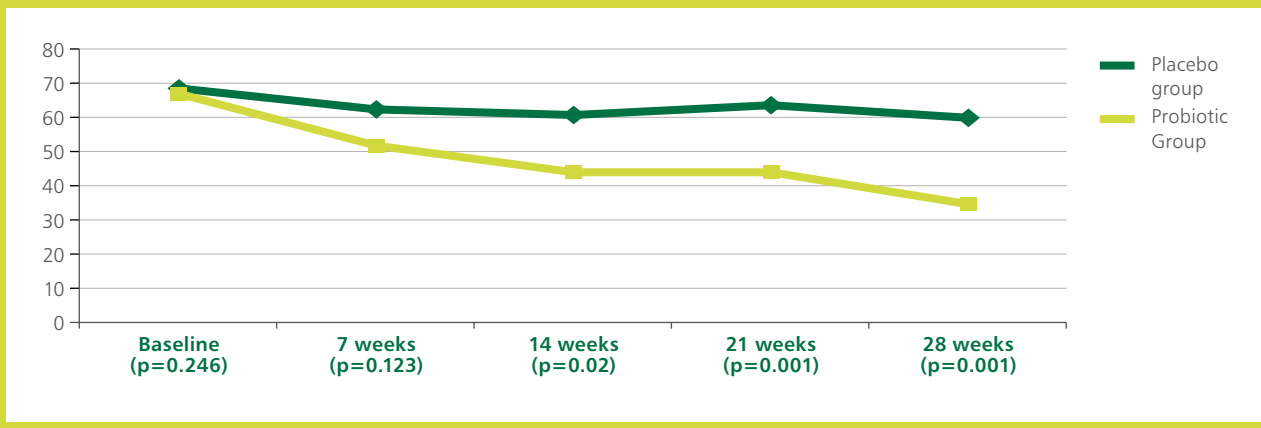
Cummulative changes in Alanine Transaminase (ALT) Levels over time (IU/L)





**Protexin probiotics significantly improved liver function in patients with Non-alcoholic Fatty Liver Disease**

**Cummulative changes in Aspartate Transaminase (AST) Levels over time (IU/L)**



in the probiotic group was significantly greater than that in the placebo group ( $P < 0.001$ ). Similar results were noted in the levels of aspartate transaminase (AST). Significant changes were observed at 21 and 14 weeks respectively, and maintained right through the 28 week assessment period.

Statistically significant improvements were also seen in both groups in Gamma-glutamyl transpeptidase (GGT) levels after 28 weeks with the mean improvement statistically greater in the probiotic group ( $p < 0.001$ ). A similar result was obtained when looking at improvements in the inflammatory markers hs-CRP and TNF- $\alpha$  with the mean improvement in both parameters greater in the probiotic group ( $p < 0.001$ ). Whilst there were also improvements in both BMI and waist to hip ratio in both groups the difference between the two groups was not significant ( $p = 0.13$ ).

### Conclusion

This randomised, double-blind, placebo-controlled trial found some evidence that probiotic supplementation in addition to lifestyle modification is superior to lifestyle modification alone for the treatment of NAFLD, at least partially through attenuation of inflammatory markers in the body. Whether these effects will be sustained with longer treatment durations remains to be determined but this trial can form the basis for further, larger and longer term studies to conclusively evaluate the potential for the use of probiotics in the management of NAFLD.

Eslamparast T, Poustchi H, Zamani F, Sharafkhan M, Malekzadeh R, & Hekmatdoost A. 2014. Synbiotic supplementation in non-alcoholic fatty liver disease: a randomized, double-blind, placebo-controlled pilot study. *The American journal of clinical nutrition*, **99**(3), 535-542.

# Effect of a Probiotic and Metformin on Non-alcoholic Steatohepatitis (NASH)

## Objective

To assess the effects of a Protexin probiotic formulation alongside conventional treatment for non-alcoholic steatohepatitis (NASH). The study primarily investigated the effects on liver enzymes & ultrasound grading of steatosis.

### The Protexin multi-strain formula

*Lactobacillus casei* PXN 37

*Lactobacillus rhamnosus* PXN 54

*Streptococcus thermophilus* PXN 66

*Bifidobacterium breve* PXN 25

*Lactobacillus acidophilus* PXN 35

*Bifidobacterium longum* PXN 30

*Lactobacillus bulgaricus* PXN 39

Fructooligosaccharide (FOS)

Total viable count per capsule  $1 \times 10^8$  CFU

## Methods

This was a double blind, randomised, placebo controlled study in 67 patients aged between 18 – 75 years with histologically confirmed NASH. Patients were randomised to take either Metformin + Probiotics or Metformin + placebo for a total of 6 months. This was alongside normal conventional recommendations for management of NASH (weight control, exercise, diet changes). Liver function was assessed using measurements of hepatic enzymes and ultrasound was performed to grade the extent of the liver disease. This was done at baseline and after treatment with monitoring throughout the 6 month period.

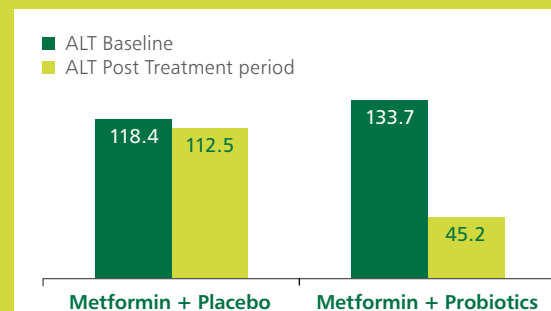
## Results

Both groups were comparable with no difference in baseline characteristics. After the treatment period there were improvements in all parameters in both groups as would be expected.

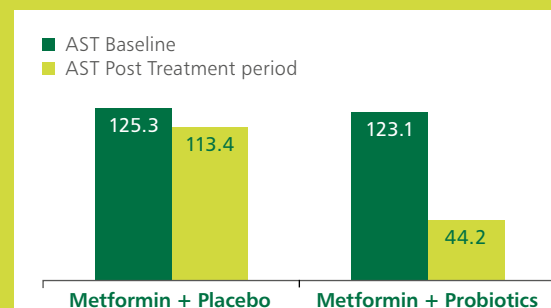
However, there was significantly greater improvement in the probiotic group with the main results summarised below:

### Effects on Liver Enzymes:

#### Effects of Treatment on ALT ( $p < 0.001$ )

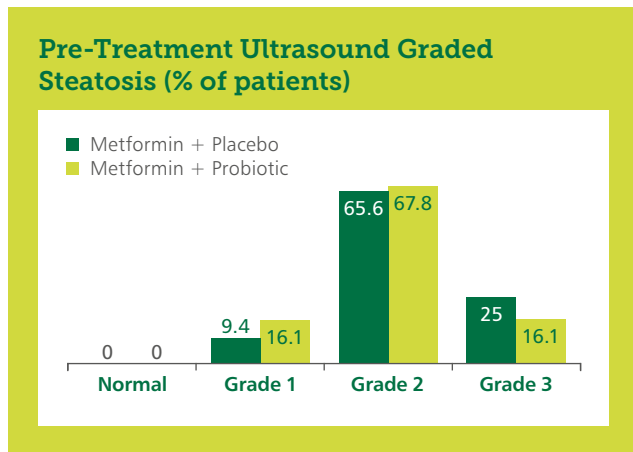


#### Effects of Treatment on AST ( $p < 0.001$ )

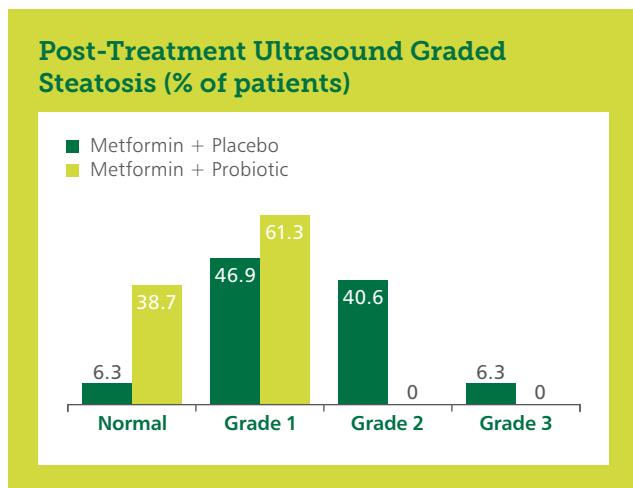


**Protexin probiotics significantly improved liver function in patients with Non-alcoholic Steatohepatitis**

**Effects on Ultrasound Grading of NASH**

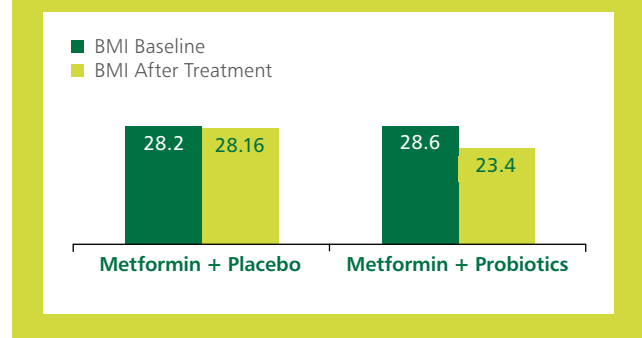


Above figure shows ultrasound graded steatosis before intervention. None of the patients had a normal grade ultrasound.



This figure shows the ultrasound grade steatosis after six months of treatment. 38.7% of patients had a normal grade ultrasound in the metformin/probiotic group; 61.3% patients had grade 1 ultrasound appearances and none of the patients had grade 2 or 3. The differences were statistically significant as compared to the Metformin/placebo group (P=0.01).

**Changes in BMI After Treatment (p < 0.001)**



The group taking the probiotic supplement alongside conventional management was found to have a significantly reduced BMI (p = 0.001) whilst the group taking placebo did not show any changes.

**Conclusion**

This study suggests that the Protexin probiotic formulation help to improve the efficacy of standard management of NASH with a number of benefits including weight loss. The mechanism of action is not fully understood, but the evidence supports the use of probiotics in the treatment of NASH and certainly supports further study to establish the exact pathways that are being influenced.

Shavakhi, A., Minakari, M., Firouzian, H., Assali, R., Hekmatdoost, A., & Ferns, G. 2013. Effect of a Probiotic and Metformin on Liver Aminotransferases in Non-alcoholic Steatohepatitis: A Double Blind Randomized Clinical Trial. *International journal of preventive medicine*, 4(5), 531-7.

# Synbiotic Preparation in Men Suffering from Functional Constipation: A Randomised Controlled Trial

Protexin probiotics significantly reduced abdominal cramps and constipation

## Objective

To evaluate the effects of a Protexin probiotic formulation on functional constipation in males.

### The Protexin multi-strain formula

*Lactobacillus casei* PXN 37

*Lactobacillus rhamnosus* PXN 54

*Streptococcus thermophilus* PXN 66

*Bifidobacterium breve* PXN 25

*Lactobacillus acidophilus* PXN 35

*Bifidobacterium longum* PXN 30

*Lactobacillus bulgaricus* PXN 39

Fructooligosaccharide (FOS)

Total viable count per capsule  $1 \times 10^8$  CFU

## Methods

A randomised, placebo controlled trial in 60 men suffering with functional constipation (FC). The men were randomised to receive either the probiotic capsule or the placebo capsule. Both capsules were identical and participants took one capsule twice a day for 4 weeks. Outcome measures were number of bowel movements (BMs) per week, the completion

of a Patient Assessment of Constipation Symptoms Questionnaire (PAC-SYM) and Bristol stool form scale.

## Results

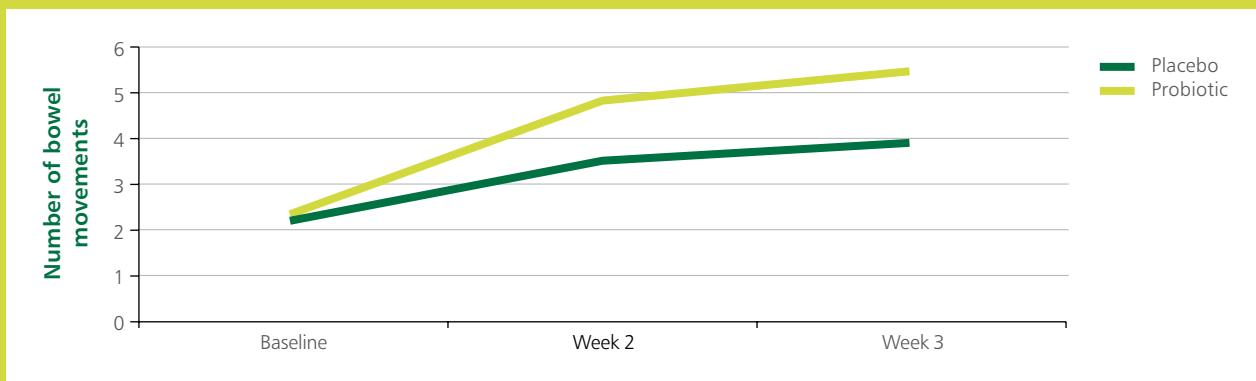
There was a significance increase in bowel movements in the probiotic group compared to the placebo at weeks two and four. BMs increased from 2.29 / week in the probiotic group to 4.81 at week two and to 5.45 BMs in week four ( $p = 0.02$ ).

There was also a significant difference seen at weeks two and four in the Bristol stool form scale ( $p = 0.0006$ ), as well as improvements in the PAC-SYM, namely reduction in stomach cramps ( $p = 0.02$ ) and reduction in the frequency of BMs being too small ( $p = 0.03$ ).

## Conclusion

This study shows that the Protexin probiotic formulation is able to significantly increase bowel movements per week as well as reducing abdominal cramps and frequency of small bowel movements in constipation sufferers. There were no side effects reported with the consumption of the probiotic in this study.

The effect of probiotic on average number of bowel movements per week in FC sufferers



Fateh R, Iravani S, Frootan M, Rasouli MR, Saadat S. 2011. Synbiotic preparation in men suffering from functional constipation: a randomised controlled trial.

Swiss Med Wkly. 141:w13239.

# Probiotics Increase Efficacy of Standard Antibiotic Treatment for Bacterial Vaginosis

Protexin probiotics significantly reduced Bacterial Vaginosis

## Objective

To compare the efficacy of metronidazole versus a combination of metronidazole and a Protexin probiotic formulation in the treatment of bacterial vaginosis.

### The Protexin multi-strain formula

*Lactobacillus casei* PXN 37

*Lactobacillus rhamnosus* PXN 54

*Streptococcus thermophilus* PXN 66

*Bifidobacterium breve* PXN 25

*Lactobacillus acidophilus* PXN 35

*Bifidobacterium longum* PXN 30

*Lactobacillus bulgaricus* PXN 39

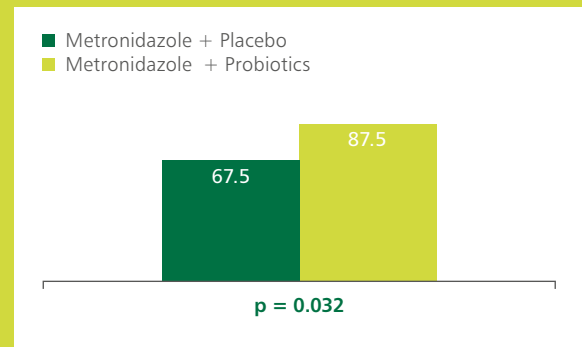
Fructooligosaccharide (FOS)

Total viable count per capsule  $1 \times 10^8$  CFU

## Methods

80 women were included in the clinical trial. Bacterial vaginosis was diagnosed using Amsel criteria. All patients were treated with a standard course of metronidazole but were randomised to receive either placebo or the probiotic formulation alongside treatment. Patients were assessed for symptoms and Amsel criteria at baseline and at 3-7 days post treatment. Treatment success was defined as the absence of any of Amsel's criteria.

### Treatment Success (%)



## Results

There was significant improvement in symptoms in both groups. Symptoms of vaginal discharge, itching, and foul smelling discharge improved in all patients. However, the probiotic group showed a higher rate of treatment success (87.5%) versus placebo (67.5%) and this was statistically significant ( $p = 0.032$ ).

## Conclusion

The inclusion of the Protexin probiotic formulation greatly increased the efficacy of treatment in this trial suggesting that it can be an effective adjunct to conventional treatment in the management of bacterial vaginosis.



Protexin®

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Volume 4 Published April 2016  
M0043-01