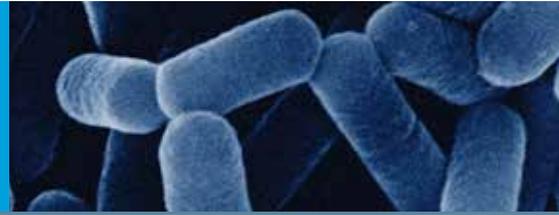


Probiotic Bulletin

A Newsletter for Healthcare Professionals

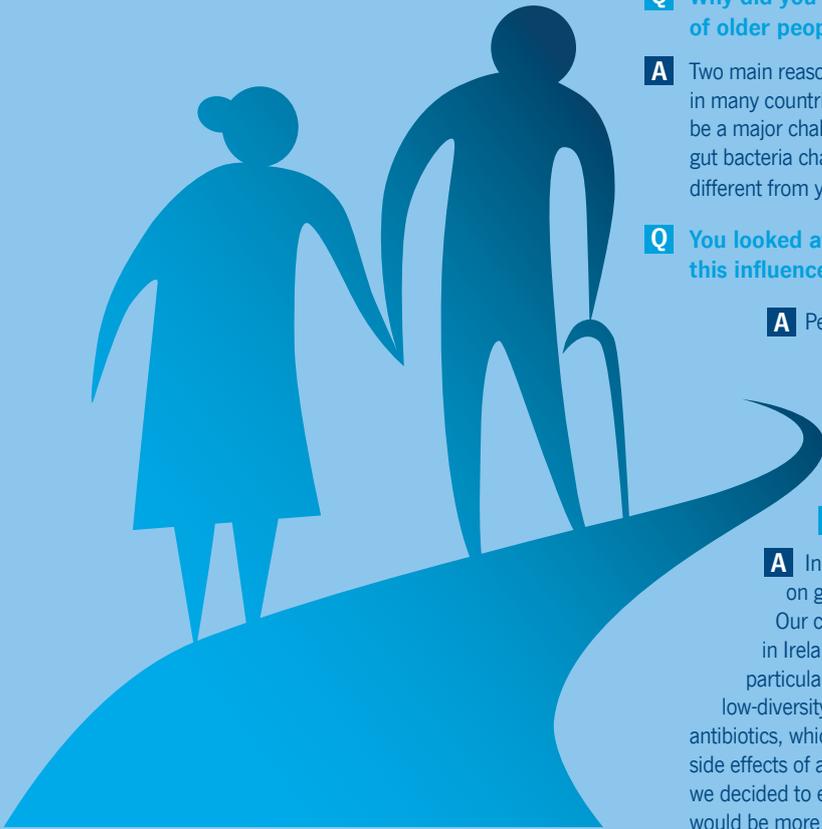


Gut microbial changes in later life

Correlations between diet, health and microbiota



Professor Paul O'Toole (University College Cork, Ireland) was amongst the eminent speakers at the recent International Yakult Symposium in London (see page 6 for full report). We caught up with him to ask about his latest work on the fascinating ELDERMET project.



Q Why did you choose to focus your research on the gut microbiota of older people?

A Two main reasons. Firstly, the proportion of people over the age of 65 is set to double in many countries over the next 30 years, so keeping these people healthy is going to be a major challenge. Secondly, there were conflicting reports in the literature on how gut bacteria change in older people, but mostly suggesting that gut bacteria were very different from younger adults, so we wanted to get a grip on that, and understand why.

Q You looked at subjects living at home and at those in residential care. Did this influence their microbiota?

A People living in their own homes and indeed those just popping into day hospital occasionally had a diverse community of gut bacteria, which was close to that found in healthy younger adults. However, those living in long-term residential care for up to six weeks, and especially those living in care longer than that, had a very different low-diversity gut bacterial community.

Q Why did you exclude anyone taking antibiotics?

A In a previous study, we found that taking antibiotics had a major effect on gut bacteria; it killed off large numbers, including those linked to health. Our colleagues in Teagasc (the agriculture and food development authority in Ireland) have recently done some nice work showing that this effect is also particularly harsh in people living in long-term residential care. It seems that the low-diversity gut bacterial community in these people is particularly sensitive to antibiotics, which is why consuming probiotics is often recommended to reduce the side effects of antibiotics. Because the more recent study was mainly focussing on diet we decided to exclude people on antibiotics, so that the effects of diet on gut bacteria would be more clearly seen.

In this issue:

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International Yakult Symposium 2013	6	Research roundup: recent papers	7	Royal Voluntary Service	7	Stop press!	8



To promote Gut Week and enter the £1,000 Gut Health Awareness Award, visit... www.loveyourgut.com/HCP
 Alternatively call: 020 8842 7600 or email info@loveyourgut.com
 For full terms and conditions please visit www.loveyourgut.com/HCP



Q&A

Interview with an expert: (continued)



Q By collecting dietary data, you identified four dietary groups. Could you tell us more?

A We called them DG1 to DG4. DG1 is the best diet (low fat, high fibre) and was most common in people living at home; DG4 is the worst diet group (high fat with moderate fibre). DG2 and DG3 were in-between. DG1 had the highest intake of fruit, fibre, pasta and oily fish; DG4 had the lowest intake of fruit, fibres, and vegetables. It also had lots of food with readily available sugar and more red meat.

Q Did the dietary groups correlate with where the subjects lived?

A The worst diet was eaten by people living in long-term residential care. I was a bit shocked by this and quickly checked the menus in two care homes, to discover that there were a lot of healthier things available on the menu than were being chosen. However, it seems that people make bad dietary choices. In some cases, this is of course due to poor dentition, lack of taste, lack of saliva production and other factors but in a lot of cases it's probably due to inadequate dietetic advice and support. These people also have the lowest-diversity microbiota.

Q Did diet cause the change in gut microbiota or vice versa?

A We showed pretty conclusively that the diet changes the gut bacteria. When people move into long-term care homes their diet changes totally within a few weeks but their gut bacteria take up to one year to change. This suggests that the diet change drives the microbiota change.

Q Did the differences in microbiota correlate with indications of health?

A We found significant links between several measures of health and gut bacteria. The strongest links were with measures of frailty and the risk of malnutrition. In addition, links were found with blood pressure and calf circumference, which may be due to

the influence of the diet and/or the microbiota on muscle mass, and the decline in muscle mass (sarcopaenia). These findings are supported by a link between frailty and the chemical markers of bacterial activity. Frailer individuals also had lower levels of the short-chain fatty acids acetate, butyrate and propionate, chemicals made by bacteria that were present in high levels in the intestines of community dwelling individuals. We also found links to inflammation, which is a common problem in older people, and makes them more susceptible to infections like winter colds.

Q Subjects in long-stay had a normal BMI, while the other three groups had an overweight or obese BMI. So, although 84% of long-term stay patients were in the unhealthy dietary groups (DG3 and DG4), they still maintained a normal BMI. Was this because they were less likely to eat enough food so it was easier to achieve their daily energy intake by giving food with a higher calorific value, which of course have less nutritional value (i.e. foods in DG3 and DG4)?

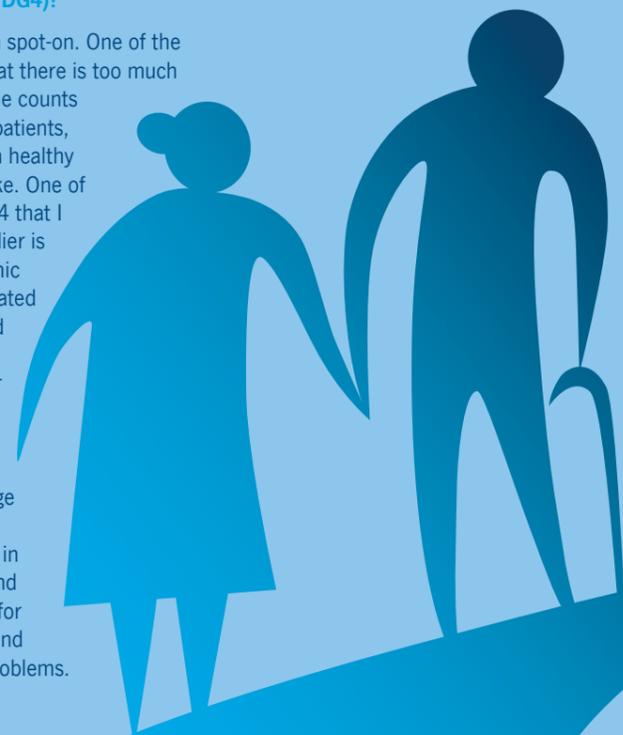
A That's pretty much spot-on. One of the issues for me is that there is too much emphasis on calorie counts in long-term care patients, and not enough on healthy food diversity intake. One of the features of DG4 that I skirted around earlier is the higher glycaemic index foods associated with it. Having said that, the high proportion of older people with a BMI that makes them technically obese is also a huge concern. It reflects the general trends in the populations, and the runaway stats for obesity, diabetes and other metabolic problems.

Q So have you any recommendations for older people?

A Resist the temptation to have a Sunday dinner every day. Try to vary your diet from day-to-day. Eat as much fruit as you are comfortable with. Drink lots of water. Don't skip dinner and don't just eat dessert. If in hospital or long-term care, talk to the ward staff and ask for dietary advice, mentioning any conditions or medications you are on.

Q Do you plan to investigate any dietary intervention with these subjects (e.g. prebiotics or probiotics) to see if there is potential to alter the microbiota composition?

A Yes we do; we plan to do this as part of the Alimentary Pharmabiotic Centre's work in Cork. We are really excited about prospects for improving gut health based on dietary interventions.



ELDERMET is a project based at University College Cork, Cork University Hospital, and Teagasc (Moorepark), funded by the Government of Ireland and the Health Research Board.

It aims to:

- Assess the faecal microbiota composition of elderly volunteers in the Irish population.
- Explore potential correlations between this and a range of health indices.
- Develop specific dietary recommendations to improve the health of the elderly consumer.
- Provide evidence-based recommendations for prospective studies to determine the molecular mechanisms for health improvements promoted by specific food ingredients that modulate components of the microbiota.

Did you know...

- There are now more people in the UK aged 60 years and above, than there are under 18¹
- 40% of all people aged over 65 years in the UK have a long-term limiting illness²
- It is estimated that 1.3 million people over 65 in the UK suffer from malnutrition; 93% live in the community³
- The colonic microbiota is thought to become increasingly perturbed with age, which may hasten the onset of certain diseases⁴
- Individuals in long-stay care have significantly less diverse microbiota compared to community dwellers⁵
- Alterations in the microbiota of older people have been associated with frailty^{5,6}
- In a study of Irish older people, *Clostridium difficile* was detected in 1.6% living in the community, 9.5% in outpatient settings and 21% of patients in hospital⁷

Reference list available at www.yakult.co.uk/hcp or from science@yakult.co.uk

| HCP Insight

The British Dietetic Association (BDA) evidence-based practice guidelines for the dietetic management of IBS in adults



The Gastroenterology Specialist Group (GSG) is a voluntary group within the BDA run by registered dietitians with a particular interest in the gut and liver. The group has nine clinical lead positions (IBD, IBS, coeliac disease, liver, pancreas, intestinal failure, enhanced recovery and upper and lower GI), and its aims are to:

- Support and develop good UK evidence-based dietetic practice within gastroenterology and hepatology.
- Provide up-to-date evidence-based information and resources on the dietary treatment of gastrointestinal and hepatic conditions for patients, the public, dietitians and other health professionals, and coordinate with relevant charities and other organisations.
- Encourage and enable continued professional development. (The GSG holds regular study days; at least two per year.)
- Provide a channel for communication and networking between dietitians in gastroenterology and hepatology, to share information and experiences.

The group's guidelines for the dietetic management of IBS in adults (McKenzie et al 2012) are currently under review. Yvonne McKenzie (IBS Clinical Lead; left in the picture) organised a competition among the dietitians involved for a free delegate place at the International Yakult Symposium. Elizabeth Bridcut was the worthy winner but as she was unable to come, Fiona Cook (also a Gastroenterology dietitian, right in the picture) was her replacement.

Probiotic use in hospitals: important considerations for certain patient groups

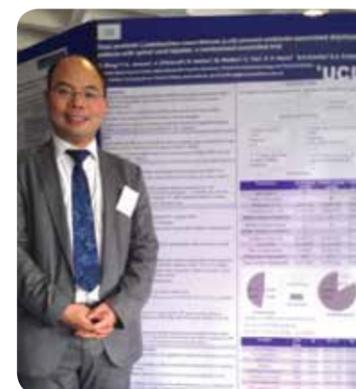
Lactic acid bacteria have a long and safe history of use, and lactobacilli and bifidobacteria are extremely rare causes of infection (Borriello *et al* 2003) but healthcare professionals think carefully when considering probiotics for patients who are seriously ill or immunocompromised. The potential risks and possible benefits must be weighed: on the one hand, severe infections are often associated with gut dysbiosis, poor gut barrier function and a high degree of systemic inflammation, but conversely, is there risk of probiotic translocation?

One clear recommendation resulted from the PROPATRIA study (Besselink *et al.* 2007, fatalities associated with bowel ischaemia not sepsis): probiotics should not be used in patients with severe acute pancreatitis or multi-organ failure.

Recently the Haematology Sub Group of The BDA Oncology Group (*Complete Nutrition*, Jan 2013) looked again at dietary advice during neutropenia. They noted that there is no evidence that lactobacilli and bifidobacteria present any greater infection risk than commensal strains and in addition highlighted the growing body of evidence suggesting that probiotics are safe in certain immunocompromised groups, such as patients with HIV and neonates. Based on uncertainty rather than robust evidence of harm, however, their advice has not changed: neutropenic patients should avoid probiotics and live yoghurt.

Case reports, intervention studies and meta-analyses describe probiotic use in seriously ill patients. Whilst many indicate potential benefit, most caution that more research is needed (e.g. a recent review co-authored by Yakult scientists; Shimizu *et al* 2013).

A list of references is available at www.yakult.co.uk/hcp or from science@yakult.co.uk



New study: antibiotic-associated diarrhoea

Patients with spinal cord injuries: interview with Dr Samford Wong

Dr Samford Wong is Clinical Lead Dietitian and Research Associate at the National Spinal Injuries Centre at Stoke Mandeville Hospital. He was awarded the Spinal Cord Prize by the International Spinal Cord Society in November 2012 for his research, and has received recognition from the Healthcare Infection Society (Mike Emmerson Young Investigator Award).

At the International Yakult Symposium, he presented results from a recent probiotic study at Stoke Mandeville Hospital (see photo). In May, he travelled to the USA to give a talk about this research to the American Spinal Injury Association (see box below). We had the chance to chat with him at the symposium to find out more.

Q What sparked your interest in patients with spinal cord injuries (SCI)?

A I like calculations. I do research in a way that I can prove there is a solution to improve a patient's quality of care. I have an interest in helping to improve the lives of SCI patients as they face overwhelming lifestyle changes.

Q The majority of SCIs occur as a consequence of road traffic accidents (RTAs) and falls. Do you think this is why around 80% of these patients are male?

A Partly, yes. RTAs (including motorcycle accidents) commonly involve men – as do surfing accidents in the summer and skiing accidents in the winter; both predominantly male hobbies. Obviously, wearing a seatbelt is the best prevention of SCI in RTAs. The majority of SCIs caused by 'falls' are actually in older people.

Q Can you describe your patients and their quality of life?

A Quality of life is a large area of research. The average stay in SCI centres is six months.

At Stoke Mandeville Hospital, patients are encouraged to participate in sports and are supported into re-employment, to achieve a meaningful life and a better quality of life.

Q Why do SCI patients often suffer urinary tract infections?

A Due to their injuries, SCI patients have neurogenic bladder, which means they have difficulties in controlling their bladder. Spinal doctors recommend their patients empty their bladder with

self-intermittent or indwelling suprapubic catheters (catheters put into the top of the bladder). However, this could leave foreign material in the bladder, which may increase the risk of infections.

Q There is a high incidence of antibiotic-associated diarrhoea in these SCI patients, so are they particularly vulnerable?

A Yes, because if they have diarrhoea, all their rehabilitation will be stopped. This not only affects the SCI patients, it also causes a lot of extra cost to the NHS. We have a very strong microbiology team, who have bought in strict rules about isolation, hand hygiene, etc.

Q Did Stoke Mandeville Hospital use probiotics during its care practice with SCI patients prior to the study?

A No, we are presenting the results to the trust board committees. We are aware of the limitation in the study (no placebo). We are very keen to run this with a placebo before making any recommendations - but saying that, we won't discourage patients from taking a probiotic.

The hospital managers are very interested in probiotic use as it could potentially reduce nursing and cleaning times. In the future we want to factor in the health economic cost.

Wong SS *et al* (2013) Do probiotics prevent antibiotic-associated diarrhoea in patients with spinal cord injuries? : A randomized controlled trial

Topics of Spinal Cord Injury Rehabilitation (2013) 19, 1: doi:10.1310/sci19S1-1

Aims This open-label study at the National Spinal Injuries Centre (Stoke Mandeville) investigated whether a probiotic (a fermented milk drink containing *Lactobacillus casei* Shirota) could help reduce incidence of antibiotic-associated diarrhoea (AAD) and *Clostridium difficile*-associated diarrhoea (CDAD) in SCI patients. The study also examined whether undernutrition and use of proton pump inhibitors (PPI) were risk factors.

Methods 164 SCI patients recently prescribed antibiotics were randomly allocated to receive either probiotic (n=79) or no probiotic (n=85). The probiotic was given once daily during antibiotic use and for seven days afterwards. Nutritional risk was assessed by the Spinal Nutrition Screening Tool.

Results The probiotic group showed a significantly lower incidence of AAD compared to the control group (17.1% vs. 52.9%, $P<0.001$). Only one CDAD case was reported, which was in the control group.

Overall, 65% of the patients were at risk of undernutrition; this and use of PPI were associated with AAD ($P<0.01$ and $P=0.022$ respectively).

Poor appetite (OR: 5.045, 95% CI: 1.283-19.84) and routine care with no probiotic (OR: 8.459; 95% CI: 3.224-22.196) were identified as independent risk factors for AAD.



The International Yakult Symposium 2013

22nd & 23rd April, London



Yakult hosts two days of high-level scientific discussion on the gut microbiota and probiotics.

Over 300 delegates from 23 countries gathered in the Queen Elizabeth II Conference Centre – some travelling quite a way to be there: from Australia, Brazil, China, India, Indonesia, Singapore, USA... and of course Japan, where the company was founded.

The first session (chaired by Prof Glenn Gibson) started with a keynote lecture from Prof Joel Doré on the human microbiome project, which has shown that humans share a core microbiome with individual differences in species, enterotypes and gut bacterial gene counts. He proposed that the gut microbiota should be considered as a separate organ in the body, and presented evidence of the link between low microbial diversity and disease risk. Dr Kenji Oishi then presented his research showing that bifidobacteria are transferred from mothers to their babies, followed by Prof Paul O'Toole on the ELDERMET project (see pages 1-3).

In the second session (chaired by Prof Lorenzo Morelli), Prof Jerry Wells described the extracellular polymeric matrix of *Faecalibacterium prausnitzii*, a strain able to occupy a unique niche in the gut mucus. An overview of gut barrier function and microbiota effects was given by Prof Stephan Bischoff and then Prof Yolande Sanz presented research into the role of the gut microbiota in coeliac disease. Dr Ailsa Hart from St. Mark's Hospital looked at the gut microbiota's involvement in IBD, showing some research into the benefits of antibiotics, probiotics and faecal transplantation.

Prof Stella Knight chaired the opening session on the second day, which started with a keynote lecture from Prof Hiroshi Kiyono on

how the gut microbiota regulates the immune response in the gut, including an explanation of gene expression in Peyer's patches, the effects of segmented filamentous bacteria and epithelial cell fucosylation. Prof Maria Rescigno further discussed the effects of gut bacteria and IBD, showing results from her group looking at probiotic effects in animal models. Prof Julia-Stefanie Frick summarised current understanding on how the gut-based immune system distinguishes pathogens from commensals, emphasising the three elements that determine outcome: the pathogen, the host and the commensals.

Prof Herbert Lochs chaired the last session, which began with Prof Harry Flint describing the major impact of diet on gut metabolites of microbial origin and the 'keystone' species that determine the gut's ability to ferment insoluble substrates. Prof Patrice Cani followed by explaining how the gut microbiota contributes to energy homeostasis, and how bacterial compounds contribute to low grade inflammation and gut permeability in obesity-related disease. Finally, Prof Frederik Bäckhed discussed his research analysing the gut metagenome of patients with type 2 diabetes, suggesting disease onset could be predicted by the gut metagenome.

Lively Q&A sessions followed each talk, and in the breaks crowds gathered around the research posters on display (more than 60), creating a buzz of scientific debate.

Here we show a gallery of images from the event, including the evening's entertainment and dinner at Church House, just over the road from the conference.

The proceedings will be submitted for publication later this year. Yakult's popular national symposium will take place in London 2014 – watch this space for the first alerts.



Ethnic diversity of the gut microbiota: the Japanese and Belgians

Scientists at the Yakult research institute in Ghent used qPCR to examine the gut microbiota of 42 Belgian adults, then compared results with samples from Japanese subjects. This showed the Belgians had a lower population size and prevalence of *Bifidobacterium catenulatum*, but overall there was no difference in bifidobacteria profile.

Ishikawa E et al (2013) *J Biosci Bioeng* [Epub ahead of print]

Reduction of uremic toxins by probiotics, prebiotics, synbiotics

This Australian review looked at two protein-bound toxins: p-cresyl sulphate and indoxyl sulphate, and concluded there was limited but supportive evidence for the effectiveness of pro- and prebiotics in the chronic kidney disease population. Of the 19 studies meeting the inclusion criteria, four were with *L. casei* Shirota (LcS).

Rossi M et al (2013) *Int J Nephrol* [Epub 2012 Dec 19]

Probiotic reduction of aflatoxin in a model system

This animal model study at the Universiti Putra Malaysia showed that dietary supplementation with *L. casei* Shirota improved adverse effects of the mycotoxin on body weight and plasma biochemical parameters, and reduced aflatoxin levels in blood serum.

Nikbakht Nasrabadi EN et al (2013) *J Applied Microbiol* doi: 10.1111/jam.12148. [Epub ahead of print]

Tip: search on 'aflatoxin' for other LcS studies on www.yakult.co.uk/hcp

Constipation study in Malaysia

This randomised, double-blinded trial involved 90 adults with functional constipation given four weeks of an LcS-fermented milk drink or placebo: there was some improvement in both groups. The probiotic group showed significant improvement for constipation severity at week 4 (P=0.058), with indications of particular effect for incomplete evacuation.

Mazlyn MM et al (2013) *J Gastroenterol Hepatol* [Epub ahead of print]

Tip: search on 'constipation' for other LcS studies on www.yakult.co.uk/hcp

Immune study in healthy older volunteers

This randomised crossover trial at the University of Reading with 30 volunteers (55-74 years), investigated the effects of four weeks' intervention with either a fermented milk drink with *L. casei* Shirota or placebo. Peripheral blood and saliva analyses showed that probiotic consumption was associated with a significant increase in natural killer cell activity plus a trend towards a less inflammatory profile. (The PhD student was partially funded by Yakult UK Ltd.)

Dong H et al (2013) *Eur J Nutr* [Epub ahead of print]

Tip: search on NK cell for other LcS studies on www.yakult.co.uk/hcp

International Life Science Institute Monograph: Probiotics, Prebiotics and the Gut Microbiota

This broad overview of current scientific understanding is written in a clear and understandable style to help inform a wide audience about the role of the gut microbiota in health and disease, the probiotic and prebiotic concepts plus their health effects and mechanisms of actions.

Binns N (2013) *ILSI Europe Concise Monograph Series* 2013:1-32

Order or download at www.ilsis.org/Europe/Pages/Prebiotics-Publications.aspx

And finally... probiotics induce a glow of health - 'because I'm worth it'?

This MIT study in the USA investigating a range of age-related changes in mice, found that probiotic consumption was associated with certain visual benefits including shinier and more luxuriant fur, which in females seemed to align with fertility.

Levkovich T et al (2013) *PLOS One* 8(1):e538.

| Just our cup of tea!

Yakult supports the Great Brew Break 2013

Royal Voluntary Service (formerly WRVS), a great British charity that helps 100,000 older people every year, is most famous for two things: its dedicated volunteers and the cups of tea they have been serving Great Britain since 1938.

Mirroring the work of Royal Voluntary Service, Yakult employs 40,000 Yakult Ladies in Japan, who, as part of their role distributing Yakult products, routinely visit and support older people within the community. Both Yakult and Royal Voluntary Service celebrated key milestones this year: Royal Voluntary Service turned 75, whilst the unique Yakult Ladies system marked its 50th year of operation in Japan.

The Great Brew Break took place from 29th April to 5th May, with tea events organised all around the country by Royal Voluntary Service's army of volunteers, service users, employees and members of the public. The money raised will help Royal Voluntary Service volunteers make life better for older people in the community. And although the official event has ended, anyone interested in helping this worthy cause can still find out more by visiting www.royalvoluntaryservice.org.uk or calling 0845 600 5885.



STOP PRESS!

Calling all healthcare professionals! NEW Gut Health Awareness Award!

The national annual Gut Week awareness campaign is organised by the digestive health charities Core and the IBS Network in association with Yakult UK Limited. The campaign this summer is celebrating its 15th year.

Gut Week provides an ideal opportunity for you to highlight digestive health issues that may otherwise be ignored, and to encourage good gut health. Campaign posters and leaflets can be supplied to your surgery, hospital or other place of work for free; simply visit www.loveyourgut.com/HCP.

Healthcare professionals are encouraged to support the campaign by entering for:

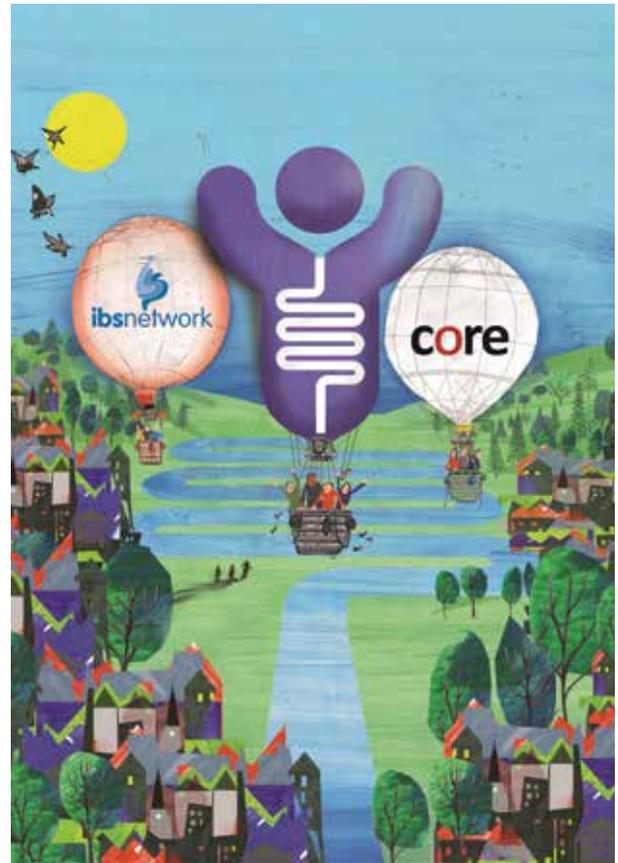
a Gut Health Awareness Award of £1000
with two runner-up prizes of £500



The award, judged by the Gut Week partners, will be based on:

- the success of the Gut Week campaign run in your clinic, surgery or hospital, plus
- a suggestion for raising awareness of the importance of gut health (optional).

For further information (including entry form, posters and leaflets), please contact info@loveyourgut.com



www.loveyourgut.com/HCP

STOP PRESS!

New research booklet!

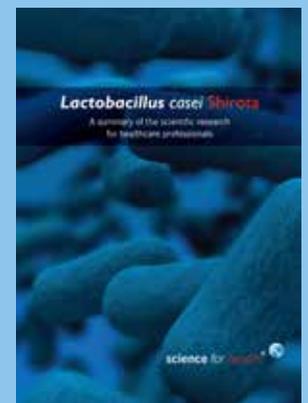
Nearly 300 peer-reviewed publications describe research into *Lactobacillus casei* Shirota, with studies from all over the world. This new HCP booklet provides a summary of:

- Fundamental research
- Immune function
- Functional gut disorders
- Emerging areas of research
- Infectious disease

To receive a free copy please contact the science team or download from www.yakult.co.uk/hcp

Contact science@yakult.co.uk for:

- ✓ Free educational talks for your department or surgery
- ✓ Advice on probiotics
- ✓ Copies of our newsletter, reprints and other material
- ✓ Free trial period of product (subject to discussion)



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New study: antibiotic-associated diarrhoea (page 5)

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Research roundup (page 7)

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