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Probiotic Bulletin

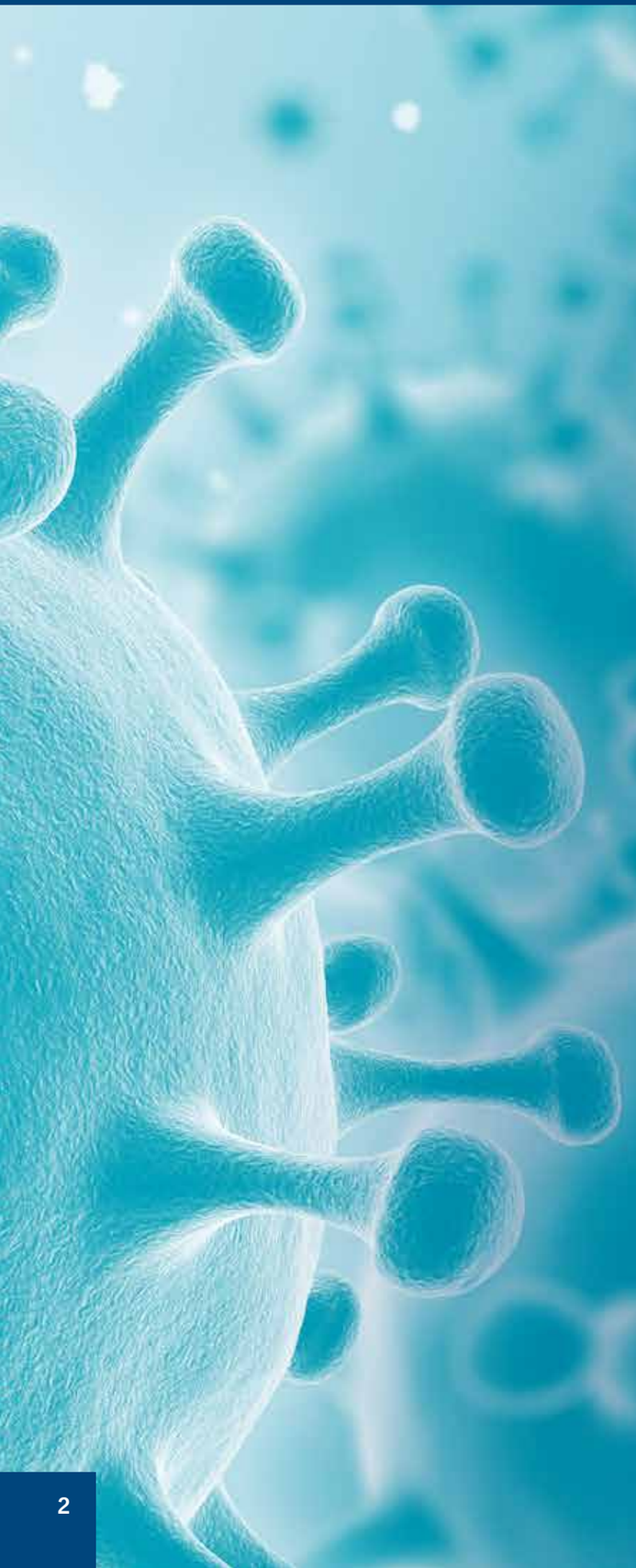
A Newsletter for Healthcare Professionals

Human immunodeficiency virus (HIV)

Does the gut microbiota have any influence on disease?

The clue is in the name – the human immunodeficiency virus (HIV) destroys or impairs the immune system. So, as the majority of the immune system is located in the gut (the gut-associated lymphoid tissue), how does HIV infection affect the commensal bacteria there (or *vice versa*), and could there be benefit from interventions that modulate the gut microbiota?

In this issue:



Dr Marcella Reale (University "G. d'Annunzio" Chieti-Pescara, Italy), a researcher in immunology, explains further: *'HIV attacks and destroys T helper lymphocytes (CD4+ T helper cells). The lower a person's CD4+ T-cell count, the more susceptible they are to infections that an otherwise healthy body could fight. Initially the decline is gradual: in the first few months and years, counts may remain near normal or only slightly decreased. But people living with HIV/AIDS (acquired immunodeficiency syndrome) face serious health threats from opportunistic infections that can be life-threatening when the CD4 count falls below 200 cells/ mm^3; these infections are the most common cause of death.'*

As early as 1993, the gut was identified as the site of significant HIV replication early in the infection process.[1] The virus disrupts the gut's barrier function and its commensal microbiota, increasing the likelihood of translocation from the gut to the bloodstream of microbial products such as lipopolysaccharide (LPS), an endotoxin found in the outer cell wall of Gram-negative bacteria.[2] The discovery that patients have elevated levels of plasma LPS[3] has implicated the gut microbiota in disease progression, because endotoxin activates the T cells that HIV preferentially targets.

Did you know….?

- In 1981, an unusual illness was first described by the US Centre for Disease Control and Prevention; the following year it was named acquired immunodeficiency syndrome (AIDS).
- In 1987 the World Health Organisation launched a worldwide campaign to raise awareness, support research, devise policies and champion the rights of patients.
- In 2008, Françoise Barré-Sinoussi and Luc Montagnier were awarded a Nobel Prize for their discovery of HIV. The US researcher Robert Gallo was later recognised as a co-discoverer.
- Public Health England reported that ~100,000 people in the UK were infected with HIV in 2012. About 21,900 did not know they were infected.[4]
- In 2013 a global HIV survey reported 1.8 million new infections, 29.2 million prevalent cases, and 1.3 million HIV-related deaths, (an improvement on 2005 results).[5]
- A three-year old child (the 'Mississippi baby'), infected at birth and treated with aggressive antiretroviral treatment (ART), has now been off treatment for more than two years and is no longer testing positive for HIV.[6]

The gut microbiota and HIV

The gut microbiome of healthy people is distinctly different from that of people living with HIV; in the latter case, it may be less diverse with loss/ reduction of key species, increased numbers/ changed profile of Gram-negative bacteria, and reduced levels of certain Gram-positive bacteria.[7-13] If diagnosed promptly, HIV can be managed with antiretroviral therapy (ART)[14-15] but even people on long term successful therapy rarely have a 'healthy' gut microbiota. Dysbiosis has been linked to disease progression, and *vice versa*. A study of newly infected, untreated men found an association between higher levels of lactic acid bacteria and higher CD4 cell count, lower viral load and reduced microbial translocation[16] (all predictors of a better clinical prognosis[17-18]).

Probiotic yogurt in Africa

A community kitchen project started in Tanzania is now being expanded across Africa thanks to the Western Heads East charity (www.westernheadseast.ca) and YobaforLife (www.yoba4life.com).[40] Professor Gregor Reid (University of Western Ontario, Canada), the main driver behind this initiative, told us: *'Probiotic yogurt that is affordable to all, has the potential to save and improve many lives in the developing world: the challenge is to get it there in a sustainable manner.'*

Professor Gregor Reid with the yogurt mamas of Mwanza

Nicholas Nduti (PhD student) and Professor Gregor Reid

The vaginal microbiota and HIV

Bacterial vaginosis (characterised by reduced numbers of the dominant commensal lactobacilli[19-20] and overgrowth with anaerobes[21]), is strongly associated with increased risk of HIV infection.[22] Normal levels of lactic acid should kill HIV; fewer lactobacilli invariably means the vagina is not sufficiently acidic.[23] A disturbed vaginal microbiota has been observed in HIV-positive women and conversely, a *Lactobacillus*-dominated microbiota has been associated with reduced HIV prevalence and viral load.[24-26] A *Lactobacillus*-predominant microbiota not only makes the vagina more hostile to HIV, it could also lower risk of transfer to male partners by reducing viral shedding. [27-28]

Probiotics and HIV

Although research is still in its infancy, interesting findings have come from investigations either into preserving immune function or improving the associated gut-related problems.[29] Such research is underpinned by mechanistic studies that have shown, for example, that expression of the CD4 receptor by lactobacilli enables these bacteria to bind to the virus and block HIV infection.[30]

In a small pilot study in Nigeria, consumption of yogurt containing *L. rhamnosus* GR-1 and *L. reuteri* RC-14 (strains previously shown to be beneficial for bacterial vaginosis)[31] was linked to cessation of diarrhoea and a trend for delayed decline of CD4 T cells.[32] A later 3-year retrospective study found that the probiotic yogurt (*L. rhamnosus* GR-1) made by local women in a low income community in Tanzania significantly increased CD4 count[33] although a large controlled study (n=112) did not show any more health benefit than that associated with consumption of a micronutrient-enriched yogurt.[34]

Probiotic studies conducted with children have also shown positive indications, including improved CD4 counts, improved growth and reduced diarrhoea.[36-38] Several other strains, a prebiotic[39] and synbiotic combinations have been investigated with adults in both developed and developing countries.[40-43]

Dr Reale and colleague Dr Falasca told us about their new research in Italy. *'Immune-modulation is an important potential mechanism for probiotics, and pro-inflammatory cytokines such as IL-6 and TNF**α**, and TGF**β** levels are elevated in HIV-infected patients, so we decided to conduct a small study in HIV-infected subjects (20 clinically stable and on ART, and 8 naive for treatment) to investigate the effects of a probiotic (*Lactobacillus casei *Shirota; LcS) on immune cell counts, and expression of cytokines in human peripheral blood mononuclear cells (PBMC) and their circulating levels in the plasma. We presented preliminary results at two conferences in Italy this year. [44] Encouragingly, we saw an average increase in CD4+, CD8+ and CD56+ cell count, and modulation of cytokine levels. The probiotic was well tolerated by the patients. Of course, larger and longer term studies are needed in order to confirm and understand these findings. It would be interesting, for example, to analyse a broader panel of immune markers, to better define their role in the HIV infection process.'*

We would like to pay our respects to the HIV/AIDS research scientists, activists and health workers who lost their lives in the recent plane crash in Ukraine, and offer condolences to all those affected.

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

The first London microbiome meeting

The first London microbiome meeting at St Thomas' Hospital in June was organised by PhD students Michelle Beaumont and Tiphaine Martin.

Talks from microbiome experts ranged from general overviews to more specific topics (eg, cardiometabolic disease, the oral microbiome and antibiotic dysbiosis). An excellent evening, an ambitious programme, and hopefully to be repeated.

Symposium report

Thomas *et al* (2014) Exploring the influence of the gut microbiota and probiotics on health: a symposium report. *British Journal of Nutrition* 112 Suppl 1:S1-S18.

This open access paper describes talks at the International Yakult Symposium in London last year. Reprints are also available from **science@yakult.co.uk.**

A consensus paper on probiotics

Hill *et al* (2014) *Nature Reviews Gastroenterology & Hepatology* **11**:506-514

Leading international probiotic experts gathered in London in October last year to re-examine the probiotic concept; this paper describes the outcome of their debate.

Apart from endorsing (but making a minor grammatical correction to) the FAO/WHO definition,[45] they distinguished three categories of these beneficial microorganisms:

- Probiotics that belong to safe species supported by sufficient evidence of general benefit in humans or with a beneficial property;
- Probiotics in food or supplements that are defined strains with proof of delivery of viable numbers at the end of shelf-life, and convincing evidence for a specific health benefit;
- Probiotic drugs: similar to the latter group but with appropriate trials to meet regulatory standards for drugs.

Undefined consortia, such as those used in faecal microbiota transplantation, were not considered to be probiotic nor were live microbial cultures used to produce fermented foods.

Yakult: Watch this space!

Yakult and the Japan Aerospace Exploration Agency (JAXA) are collaborating on a research project in the International Space Station that will last until 2020.

They will investigate whether *Lactobacillus casei* Shirota can help support the immune function and gut microbiota of astronauts living in space for extended periods.

Love Your Gut Cookery School – Cooking for a Sensitive Gut

Earlier this summer, on behalf of the Love Your Gut partners (Yakult UK Limited, Core and the IBS Network), we organised an innovative Cookery School event entitled 'Cooking for a Sensitive Gut'. Based on a concept devised by Dr Nick Read of the IBS Network, the aim was to educate and inform guests about food sensitivity and intolerance, specifically with regard to digestive symptoms.

Up to 33% of the UK's adult population is estimated to have some form of food intolerance; and a 2010 survey found that 43% of the UK experience digestive discomfort (YouGov; n=2,287). Of these, 41% had never visited a doctor, which increased to 61% in 25-35 year olds. Compared to men, women experienced more constipation (53% vs 32%), bloating (62% vs 41%), flatulence (47% vs 41%) and pain (67% vs 58%).

The Cookery School was led by chef and nutritionist Dr Joan Ransley, who had devised a range of original recipes designed to be gentle on the gut – whilst still tickling the taste buds!

Love Your Gut Cookery School guests

Joan led the assembled guests (healthcare professionals, bloggers and food journalists) through a lively demonstration of a starter, main course and dessert, explaining why certain foods might aggravate a delicate digestive system, and suggesting clever 'gut-friendly' alternatives. Guests then paired off and cooked the meals for themselves within the bright and airy surroundings of Cactus Kitchens, home to Michel Roux Jr's Cookery School and Saturday Kitchen. Two nutritionists also answered questions and provided additional advice. The event ended with all guests enjoying the food they had prepared.

To see the recipes, tips – and even a video of the event – please visit www.loveyourgut.com/recipes.

FODMAPs and irritable bowel syndrome (IBS): an examination of the evidence

Staudacher HM *et al* (2014) *Nature Reviews Gastroenterology & Hepatology* **11**:256-266

Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) are short-chain carbohydrates that reach the colon undigested, where they are fermented rapidly by the commensal bacteria that reside there. As they are small molecules, they are also osmotically active in the gut.

The low FODMAP diet has become increasingly popular since the concept was first explored by researchers in Australia. [46-47] This informative review from the dietetic group at King's College London explains (with the help of a clear diagram) how these compounds trigger gastrointestinal symptoms, and summarises the clinical evidence for dietary exclusion of fermentable carbohydrates. Ten clinical studies are cited, ranging from retrospective uncontrolled trials to two of randomised, blinded, controlled, crossover design; all report benefit for one or more symptoms. The review concludes with a discussion of the difficulties of conducting such trials, and acknowledges the need to investigate how the diet may affect patients' nutritional intake and their gut microbiota, in particular bifidobacteria.

Coral reef - probiotics: a new line of research?

Coral reefs are home to an extremely diverse fauna; over 25% of marine species may live in these 'sea rainforests'. [48-50] White Band Disease is killing reefs in the Caribbean, and a University of Derby team has identified three bacteria and one ciliate as possible culprits. Although antibiotics could be a control strategy, large-scale dosing of reefs is not feasible and would increase antibiotic resistance. Coral is similar to the gut in that it produces mucus and has a commensal microbiota that is disrupted when the reef is diseased. This suggests another strategy, as lead researcher Dr Michael Sweet commented: *'We'd like to try and develop a probiotic, basically like a Yakult, where you can dose a coral that has a disease with a community of healthy good bacteria and let the coral fight off the pathogen itself.'*

Pint of Science

It's official - science is cool!

The 'Pint of Science' festival, which combines cutting-edge science talks with a trip to the pub, enables researchers to discuss their work with the general public.

We were delighted to sponsor one of the 'Understanding our Bodies' events in London this May, with talks from University College London researchers Dr Nathan Davies (*Loving your liver – why we should all become hepatophiles*) and Dr Jane MacNaughtan (*Better bacteria for a better you*).

For further details, visit **www.pintofscience.com**

These 'friendly bacteria' are music to our ears!

We were delighted to see that British DJ and music producer mr. scruff's new album is entitled 'Friendly Bacteria' and features an image of some very friendly-looking bacteria!

To listen to his music and for further details visit: **http://www.mrscruff.com/**

Crowdsourcing – helping fight ash dieback disease

The power of the people is helping researchers analyse genetic data from the fungal pathogen (*Hymenoscyphus fraxinea*) and the trees themselves (*Fraxinus excelsior*).

Get involved by going to **oadb.tsl.ac.uk** and playing the Fraxinus Facebook game, an initiative of The Sainsbury Laboratory, Norwich. Each contributor will be acknowledged.

L to R: Allan Downie, Anne Edwards, Dan MacLean, Sophien Kamoun, Kentaro Yoshida, Dianne Saunders.

Nursing Standard Awards

This year marked the 25th anniversary for these awards - and Yakult was proud to sponsor the 'Patients' Choice Award.'

Congratulations to Susan Lovett, an oncology nurse at the Shrewsbury and Telford Hospital NHS Trust, who won for the 'unbelievably kind and empathetic care' she gave to a patient and his family.

L to R : Katie Griffith (Yakult); Jane Cummings (Chief Nursing Officer, NHS England); Susan Lovett (award winner); Professor Viv Bennett (Director of Nursing, Public Health England); Fiona Phillips (TV presenter and journalist)

Love Your Gut campaign: an update from our partners

The IBS Network has just launched an e-newsletter, *The Inside Story*, for healthcare professionals interested in IBS. It contains a leading article by an IBS opinion leader/ practitioner, an editorial on a controversial topic, and notices of key publications and meetings on IBS.

Take a look at their new healthcare professionals' page at: **www.theibsnetwork.org/healthcare-professionals/** and sign up for a free copy.

Core is a national charity that funds medical research into the prevention, cure and treatment of digestive disorders, and provides information for patients and sufferers.

Check out their recent event Exploring the Science of Digestion at: **www.corecharity.org.uk/video**

Recent studies, including those with *Lactobacillus casei* Shirota (LcS)

Abdominal symptoms in patients with part or all of their stomachs removed

This study involved 134 gastrectomised patients, who were given a daily probiotic (LcS) or placebo for four weeks. The probiotic (compared to placebo) group showed an improvement in the degree of constipation, for those who had been suffering from it. The group who had been suffering diarrhoea also showed an improvement (probiotic; comparison between pre- and post-intervention).

Aoki *et al* (2014) *Scand J Gastroenterol* 49(5):552-63.

A retrospective look at habitual consumers of probiotics

This study compared women who worked for a probiotic company and routinely took probiotics, with women who did not regularly take any probiotic. The probiotic strains (LcS and *Bifidobacterium breve* Yakult [BbY]) were detected more frequently in the probiotic group's faecal microbiota, which had a profile generally considered more conducive to health. The habitual probiotic consumers were observed to have a better bowel habit (ie, increased defecation frequency and significantly softer stools, within the normal range).

Tsuji *et al* (2014) *Int J Probiotics Prebiotics* 9(1/2):31-38.

Patients with chronic kidney disease

Thirty-one patients enrolled into this exploratory randomised controlled trial; they were divided into two groups and given different doses of probiotic (LcS) for eight weeks. The higher dose of LcS was associated with a reduction of over 10% in blood urea concentrations (compared to baseline).

Miranda Alatriste *et al* (2014) *Nutr Hosp* 29:582-590.

Dysbiosis in patients with type 2 diabetes (T2D)

The faecal gut microbiota of 50 patients with T2D and 50 control subjects was analysed using a reverse transcription-quantitative PCR method. The patients had lower counts of *Clostridium coccoides* group, *Atopobium* cluster and *Prevotella*, and higher lactobacilli counts. Gut bacteria were also found more often in the blood of the patients, suggesting translocation from the gut had occurred.

Sato *et al* (2014) *Diabetes Care Aug*;37(8):2343-50

Does small intestinal permeability deteriorate with age?

In this cross-sectional study, 215 non-smoking healthy adults went on a 12-hour fast, then consumed lactulose and mannitol. This was followed by an analysis of their urine for the sugars. Gut permeability was similar for older and younger adults, but the gut appeared impaired in people who had a combination of low-grade inflammation and noninsulin-dependent type 2 diabetes.

Valentini *et al* (2104) *Physiological Reports* 2(4):e00281.

Babies undergoing surgery for congenital heart disease

This pilot study investigated 21 neonates, randomised to receive either enteral probiotic (BbY) or not. The probiotic appeared to be safe, and improved the faecal microbiota and faecal levels of organic and acetic acids. There were indications that it helped postoperative recovery.

Umenai *et al* (2014) *J Intensive Care* 2:36.

Yakult-FINA consensus statement on nutrition for the aquatic sports

These recommendations were agreed by an international panel of nutrition experts, and explain the importance of an effective nutrition plan, with specific advice for different disciplines: swimming, open water swimming, water polo, diving and synchronised swimming.

Mountjoy *et al* (2014) *Int J Sport Nutr Exercise Metab* **24(4)**:349-350.

Malnutrition in children damages the gut microbiota

In this study in Bangladesh, nutritional supplements were given to children with severe acute malnourishment in Bangladesh (for 1.3 ± 0.7 weeks). Whilst the children did gain weight, only a temporary improvement in the profile of their poorly-developed gut microbiota was observed. The association of severe acute malnutrition to significant relative microbiota immaturity may explain why such children often fail to grow normally, and indicates that nutritional supplementation should be long-term. And/ or adding gut microbes may be needed.

Subramanian *et al* (2014) *Nature* 510:417-421.

Is an aberrant gut microbiota a risk factor for sudden infant death syndrome (SIDS)?

The intestinal microbiota of SIDS babies was analysed and compared with faecal analysis of live babies. Dual colonisation with *Clostridium difficile* and *Clostridium perfringens* occurred more frequently in SIDS babies, who were also more often colonised with *Staphylococcus aureus*.

Highet *et al* (2014) *Int J Med Microbiol* 304:735-741.

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