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Is there any proof that using the mucosal immune support programme will prevent Influenza A(H1N1) 2009?

The Influenza A(H1N1) 2009 is a novel strain - there is no empirical data of consequence available on 'any intervention', either treatment or prevention.

What **is** being looked at by researchers and clinicians are mechanisms of infection and whether the experiences of prior influenza infections may confer reasonable expectations on treatments ranging from the antivirals and immunisation. For practitioners focussed on the role of nutrition in health, we have explored what we know about mucosal barrier function (the primary site of infection) and a mix of animal, human and epidemiological studies. Having reviewed these we developed a hypothesis of intervention using a safe supplementation programme.

This rationale was also used to justify the liberal recommendation for Tamiflu and for the expected rapid deployment of vaccination, and the following explanation was taken from the article in PLOS medicine (link).

In recent years a hierarchy of the quality of evidence has been increasingly promoted, particularly for the formulation of guidelines. "Hierarchies place randomised controlled trials (RCTs) at their summit, with various forms of observational studies nestling in the foothills," says Rawlins[1], but information from observational studies and other foothill inhabitants (experimental investigations, analogy with similar conditions and processes, pathological and pharmacological understanding and reasoning, and a derived assessment of risks and benefits) is also valuable.

1. Rawlins M (2009) De testimonio: On the evidence for decisions about the use of therapeutic interventions. Lancet 372: 2152–2161. Find this article online

Small numbers of patients are starting to demonstrate resistance to Tamiflu. Caution in over prescription should be recommended to all healthcare professionals to reduce the risk of early genetic modification.

I see the theory but does it really have any clinical value?

It is true to say that the recommendations are – as a combined suggestion – hypothetical. Prevention requires long studies to be sure that the cause and effect can be linked. Vitamin D does however, have at least 6 studies that show an inverse relationship between colds and flues and 25(OH)D levels or exposure to sunshine. Prevention is common sense in the main but improving the barrier function for respiratory and gastrointestinal tissues is reasonable and has a growing collection of evidence to support it.

1. Laaksi I, Ruohola JP, Tuohimaa P, Auvinen A, Haataja R, Pihlajamäki H, Ylikomi T. An association of serum vitamin D concentrations < 40 nmol/L with acute respiratory tract infection in young Finnish men.Am J Clin Nutr. 2007 Sep;86(3):714-7. View Abstract View Full Text
2. Karatekin G, Kaya A, Salihoğlu O, Balci H, Nuhoğlu A. Association of subclinical vitamin D deficiency in newborns with acute lower respiratory infection and their mothers. Eur J Clin Nutr. 2009 Apr;63(4):473-7. Epub 2007 Nov 21. View Abstract

3. Ginde AA, Mansbach JM, Camargo CA Jr. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2009 Feb 23;169(4):384-90. View Abstract
4. Wayse V, Yousafzai A, Mogale K, Filteau S. Association of subclinical vitamin D deficiency with severe acute lower respiratory infection in Indian children under 5 y. Eur J Clin Nutr. 2004 Apr;58(4):563-7. View Abstract
5. Termorshuizen F, Wijga A, Gerritsen J, Neijens HJ, van Loveren H. Exposure to solar ultraviolet radiation and respiratory tract symptoms in 1-year-old children. Photodermatol Photoimmunol Photomed. 2004 Oct;20(5):270-1. View Abstract
6. Talwar SA, Aloia JF, Pollack S, Yeh JK. Dose response to vitamin D supplementation among postmenopausal African American women. Am J Clin Nutr. 2007 Dec;86(6):1657-62. View Abstract View Full Paper

Where possible clinicians should not rely on a single study to make a prescriptive decision. Like evolution or relativity, the validity of therapies should be verified from reproduced, multiple independent sources of evidence. This is not always possible for many reasons, so collected data must be considered in the light of absence of the perfect collection of Randomised Controlled Trials (RCT's) – the current top of the hierarchical tower of confidence of effect.

Is there any evidence for the 'reduction in epithelial permeability'? Can it be measured empirically?

Under the SigA summary I mention that epithelial permeability can be improved with adequate production of SigA through the use of Saccharomyces Boulardii. This relates to the GI tract mainly, as this is the area where alterations in the permeability of these tissues is increasingly understood to be of importance. This can be measured empirically by using a lactulose and mannitol test. This looks at both tight junction and cross membrane transmissions.

1. Barrett KE. New ways of thinking about (and teaching about) intestinal epithelial function. Adv Physiol Educ. 2008 Mar;32(1):25-34. View Abstract View Full Paper
2. Turner JR. Molecular basis of epithelial barrier regulation: from basic mechanisms to clinical application. Am J Pathol. 2006 Dec;169(6):1901-9. View Abstract View Full Paper
3. Dastych M et al.Lactulose/Mannitol Test and Specificity, Sensitivity, and Area under Curve of Intestinal Permeability Parameters in Patients with Liver Cirrhosis and Crohn's Disease. Dig Dis Sci. 2008 Mar 5 [Epub ahead of print]

Saccharomyces Boulardii promotes the production of barrier defence mechanisms outside of the production of SigA – these are the polyamines – spermine in particular. Polyamines and their acetylated derivatives are a prerequisite for cellular metabolism and considered to be essential for proliferation and differentiation of the rapidly renewing intestinal mucosa. These polyamines have a role to play in the quality of barrier function, and endogenously stimulated spermines confer barrier permeability benefit.

1. Costalos C, Skouteri V, Gounaris A, Sevastiadou S, Triandafilidou A, Ekonomidou C, Kontaxaki F, Petrochilou V. Enteral feeding of premature infants with Saccharomyces boulardii. Early Hum Dev. 2003 Nov;74(2):89-96. View Abstract

What does vitamin D do to the barrier function?

This relates to Vit D receptor triggering of cathelicidins and defensins. These are locally produced (in the mucosa) and in the skin through monocytes, and neutophils. Vitamin D3 enables the Toll Like Receptors (TLR) including the 'virally' relevant TLR3 to recognise pathogens and respond by increasing innate defence production.

In a recently published paper, Epidemic Influenza and Vitamin D (PDF download), the authors document the evidence that epidemic influenza, and even some of the viruses that cause the common cold, may be prevented by adequate doses of vitamin D. *The Independent* ran a feature article on this paper and Medical News Today printed a detailed article about how the observations were made, the theory developed, and the paper written.

1. Hansdottir S, Monick MM, Hinde SL, Lovan N, Look DC, Hunninghake GW. Respiratory epithelial cells convert inactive vitamin D to its active form: potential effects on host defense. J Immunol. 2008 Nov 15;181(10):7090-9. View Abstract

What numbers of people were involved in the colostrum study, was it on H1N1 (Swine Flu)?

This is fully available on the educational site as a download paper.

In Part 1 of the study, 144 healthy individuals of both sexes (age range, 30 to 80 years) were included and divided into 4 groups. Two similar groups were formed by subjects who underwent flu vaccination within 2 weeks before the inclusion: one group of 44 subjects took colostrum, and the other group of 39 did not take any type of immunostimulant or antiviral drug. A third comparable group of 38 subjects received only colostrum, without a flu vaccination. The prophylaxis groups were compared with a fourth group of 23 subjects who did not use any prophylaxis.

The second part of the study included very-high-risk subjects (end-stage coronary patients, patients with pulmonary hypertension or severe cardiovascular problems). Of a group of 65, 60 completed the study: 21 were treated with colostrum, 20 with vaccination in association with colostrum, and 19 with vaccination only. The prophylaxis groups were clinically comparable for age and sex distribution.

These study groups were 'clinically' relevant even though for a clinical trial the numbers are too small to draw a complete conclusion of effectiveness. I felt it was worthy of inclusion as the risk to benefit ratio was firmly in favour of benefit. This number of people is generally considered to be enough to demonstrate proof of concept and encourages further studies into the use of colostrum for influenza prevention.

Naturally this study is not on the H1N1 A 2009 virus as it has not been present in population groups for long enough. Influenza attachment and viral replication uses the same mechanisms, except that the new strain seems also prone to gastrointestinal (GI) adhesion. Approximately 40% of infected

individuals have reported GI symptoms and vomiting which is higher than that reported for seasonal influenza.[1]

1. Daewood, FS et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans N Engl J Med. 2009 Jun 18;360(25):2605-15. Epub 2009 May 7. View Abstract and Free paper

How much vitamin D is being recommended for children – isn't that a high level?

The recommendations for children 2-13 are that they take, by mixing sunlight exposure and or supplements a daily total of 4-5,000iu per day. This, based on current UK RDA levels of 5mcg or 200iu represents a 20-25 x minimum requirement to meet deficiency, or under the newer RDI level (400iu) from the USA it represents a 10-12 x dose. It should be noted that even this level is under review at present and has been for two years. The new proposed level is 1000iu. The recommendations fall comfortably inside any safety parameters for the time being. See chart.

In 2008, the American Academy of Paediatrics (AAP) issued recommended intakes for vitamin D that exceed those of Food Nutrition Board [1]. The AAP recommendations are based on evidence from more recent clinical trials and the history of safe use of 400 IU/day of vitamin D in paediatric and adolescent populations. AAP recommends that exclusively and partially breastfed infants receive supplements of 400 IU/day of vitamin D shortly after birth and continue to receive these supplements until they are weaned and consume ≥1,000 mL/day of vitamin D-fortified formula or whole milk.

1. Wagner CL, Greer FR, and the Section on Breastfeeding and Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. View Abstract

Are vitamin D toxicity fears warranted?

Is vitamin D toxic? Not if we take the same amount nature intended when we go out in the sun. Vieth[1] demonstrated that we make about 10,000iu when we go out in the sun uncovered for 20 minutes.

In 1999, Vieth indirectly asked the medical community to produce any evidence 10,000 units of vitamin D a day was toxic, saying "Throughout my preparation of this review, I was amazed at the lack of evidence supporting statements about the toxicity of moderate doses of vitamin D." He added: "If there is published evidence of toxicity in adults from an intake of 250 ug (10,000 IU) per day, and that is verified by the 25(OH)D concentration, I have yet to find it."

All ingested items have a dose related toxicity risk. This is a well understood correlation in medicine. The human intake of vitamin D3 required to achieve the equivalent toxic level to kill rats equates to a 110-pound adult taking 176,000,000 IU or 440,000 of the 400 unit cholecalciferol (D3) drops at once.

Reinhold Vieth is recognised as one of the leading researchers in the world on Vitamin D and reports human toxicity probably begins to occur after chronic daily consumption (over several years) of approximately 40,000 IU/day (100 of the 400 IU drops per day)

Heavy sun exposure when combined with excessive supplement use is a theoretical risk for vitamin D toxicity, but if such a case has been reported, I am not aware of it.

It is true that a few people may have problems with high calcium due to undiagnosed vitamin D hypersensitivity syndromes such as primary hyperparathyroidism, granulomatous disease, or occult cancers, but a blood calcium level, PTH, 25(OH)D, and calcitriol level should help clarify the cause of the hypersensitivity.

Unlike anything else used in the fortification of foods, the purpose of vitamin D is to correct an environmental deficit (less ultraviolet exposure) and not to correct for lack due to classical nutritional reasons. With a few exceptions reviewed by Takeuchi et al, there is little or no vitamin D in the kind of foods that humans normally eat. Therefore, conclusions about the efficacy and safety of vitamin D must be in the context of the role of environmental factors.

1. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentration, and safety. Am J Clin Nutr. 1999;69:842–56. View Abstract View Full Paper
2. Takeuchi A, Okano T, Ishida Y, Kobayashi T. Effects of dietary vitamin D intake on plasma levels of parathyroid hormone and vitamin D metabolites in healthy Japanese. Miner Electrolyte Metab 1995;21:217–22. View Abstract

How can you ensure optimal vitamin D status?

There are 3 ways for adults to insure adequate levels of vitamin D:

- Regularly receive midday sun exposure in the late spring, summer, and early autumn, exposing as much of the skin as possible. Limit exposure to 30 mins per day without suitable sunscreen
- Regularly use a sun bed (avoiding sunburn) during the colder months. Albeit that this has its own risks
- Take 5,000iu per day for three months, then obtain a 25-hydroxyvitamin D test. Adjust your dosage so that blood levels are between 50–80 ng/mL (or 125–200 nM/L) year-round.

How do you justify the use of varied evidence to support these recommendations?

Randomised controlled trials (RCTs) are considered to provide the best evidence but even this model has been questioned by the original promoters:

Alejandro R Jadad and Murray W Enkin, two of the great advocates of randomised trials, have written: *"Our main wish, from which all others stem, is that RCTs be taken off their pedestal, their exalted position at the top of an artificial evidence hierarchy, that all forms of evidence be appreciated for what they can offer".*

1. Jadad AR, Enkin MW. Randomized controlled trials: questions, answers and musings. 2007Oxford: Blackwell Publishing;

But what if the evidence from controlled trials is insufficient, or there simply isn't any? Guidance and specific recommendations are still potentially relevant especially in a risk to benefit discussion. The risks in the recommendations are negligible and the benefits must be considered in light of each individual's choice. It is not meant as public health policy but as a collected review for personal consideration.

An evidence-based purist might argue – this isn't unbiased information: such information is scientifically uninterpretable. The crucial question, however, is whether it's better than nothing. I believe it is.

Back to Swine flu, to date it has been at its most devastating in the sunny rural communities of the Mexican desert, not what you would expect if vitamin D deficiency is the motivator?

I agree that this is an interesting observation. However, because humans obtain most vitamin D from sun exposure and not from diet, a varying percentage of any population is vitamin D deficient, at any time, during any season, at any latitude, although the percentage is higher in the winter, in the aged, in the obese, in the sun-deprived, in the dark-skinned, and in more poleward populations. Seasonal variations of vitamin D levels even occur around the equator and widespread vitamin D deficiency can occur at equatorial latitudes, probably due to sun avoidance, rainy seasons, and air pollution. A varying percentage of most populations even equatorial ones will have impaired innate immunity at any given time, together with distinct seasonal variations in that percentage. The effects such impairments have on influenza transmission are unknown.