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ALLIANCE FOR NATURAL HEALTH
AVIAN INFLUENZA EXPERT COMMITTEE

THE PIVOTAL ROLE FOR NATURAL PRODUCTS IN COUNTERING AN AVIAN INFLUENZA PANDEMIC

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"The 1918 has gone: a year momentous as the termination of the most cruel war in the annals of the human race; a year which marked, the end at least for a time, of man's destruction of man; unfortunately a year in which developed a most fatal infectious disease causing the death of hundreds of thousands of human beings. Medical science for four and one-half years devoted itself to putting men on the firing line and keeping them there. Now it must turn with its whole might to combating the greatest enemy of all - infectious disease."

- Extract from the final edition of the *Journal of the American Medical Association*, 1918 (28 December 1918).

"All truth passes through three stages.
First, it is ridiculed.
Second, it is violently opposed.
Third, it is accepted as being self-evident."
- Arthur Schopenhauer
German philosopher (1788 - 1860)

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1. EXECUTIVE SUMMARY

This report, prepared by the Alliance for Natural Health (ANH) Avian Influenza Expert Committee, comprising leading doctors and scientists in the fields of clinical nutrition, agriculture and sustainability, sets out to evaluate the scientific evidence-base for use of nutritional and other natural product interventions in the event of a highly pathogenic avian influenza (HPAI) pandemic initiated by human-adapted forms of the H5N1 virus.

- International governments and the World Health Organization (WHO) have developed pandemic contingency and containment plans, with the use of vaccines and antiviral drugs at their core. However, it is recognised by the WHO and other bodies and research institutes that these two strategic tools have some severe potential weaknesses and vulnerabilities. These weaknesses range from the likely lack of effective vaccines in the early stages of a pandemic, to the risk of multiple pandemic viral strains emerging, complicating vaccine development and utility; additionally, shortages and limited effectiveness of anti-viral drugs are a serious issue, and there is considerable potential for the emergence of viral drug resistance once such drugs are used widely as treatments. This report further highlights, with supporting peer-reviewed scientific evidence, how government-proposed vaccination and anti-viral drug therapies could fail spectacularly, especially if these interventions are used in isolation without inclusion of nutritional protocols.

- Based on available, primarily peer-reviewed, published research, as well as the clinical experience of medical doctors on the Committee, three nutrients in particular, namely zinc, vitamin C and vitamin A, have been singled out on the basis of their importance and benefit as prophylactic and treatment agents in the event of a pandemic. In addition, unlike some of the botanical products, scaling up manufacture of these nutrients to cater for global needs during a pandemic is unlikely to be a major constraint. The scientific rationale for the supporting role of other micro-nutrients, such as B12 and selenium, has also been presented.

- Dosage requirements for key nutrients, both for prophylactic and treatment use, have been proposed in the report, these being sometimes well in excess of Recommended Nutrient Intakes (or Recommended Daily Allowances) which are used widely by governments and health authorities as measures for assessing sufficiency of micronutrient intake in populations. In the cases of both zinc and vitamin C, the report presents detailed scientific argumentation demonstrating the flawed science on which these government-accepted thresholds for micronutrient intake have been based.

- The report also considers the potential use of a range of botanical and micro-organism-derived products for which there is evidence for immune support or modulation effects. Products as diverse as beta glucans derived from yeast or mushrooms, resveratrol from the skins of grapes or berries and garlic are included. Furthermore, the report provides evidence for the potential use of various combinations of natural products as prophylactic or treatment agents, these acting on various different sectors of the immune system. However, further research is required to evaluate optimum combinations of specific nutritional and botanical or micro-

organism-derived products to combat high pathogenicity human forms of H5N1.

- A thorough review of national, WHO and other pandemic preparedness plans has shown that, to-date, there has been inadequate consideration of dietary and lifestyle recommendations for pandemic scenarios. Since normal diets may be compromised significantly during a severe pandemic, it is even more important than in a non-pandemic situation that guidance is provided to the public to ensure that general and immune system health is maintained both prior to and during a pandemic. Specific dietary and lifestyle guidance is offered in the report.

- The final section of the report contains detailed conclusions and recommendations that include three specific nutritional protocols developed by the British Society for Ecological Medicine explicitly for the purpose of prophylaxis, as well as self-treatment and medical treatment of severe respiratory illness such as that induced by high pathogenicity H5N1.

- A comprehensive series of recommendations are given, including the need to implement nutritional therapies in human cases of H5N1 infection, the need to prioritise the scaling up of micronutrient supply for a pandemic, the dissemination of dietary and lifestyle guidelines to help support the immune system, and the identification of a wide range of research requirements.

For a variety of reasons, there has long been a culture of dismissal and neglect amongst governments and their regulatory and health authorities, in respect of the role that nutrient interventions play in human health and disease. The ANH Expert Committee on Avian Influenza stresses that the dismissal of nutritional therapies by these authorities could contribute to the unnecessary loss of tens of millions of lives, and that it is therefore vital that such scepticism, however it has arisen in the past, should be discarded and the data considered objectively and rationally. The WHO and national pandemic preparedness plans should therefore be urgently revised to take these factors into account, and the appropriate nutritional plans and protocols should be included as a standard part of pandemic influenza mitigation, prevention and management.

The Committee asserts that if this does not occur, such a dismissal may come to be seen as one of the greatest acts of professional negligence in human history.

2. JUSTIFICATION FOR USE OF NATURAL PRODUCTS TO SUPPORT THE IMMUNE SYSTEM DURING AN AVIAN INFLUENZA H5N1 PANDEMIC

2.1 The pandemic threat

The timeline for the spread of the deadly H5N1 virus, as published by the World Health Organization (WHO)[1] demonstrates clearly that the virus has become endemic among wild bird populations in many parts of the world and has subsequently infected a wide range of domestic and wild animals including poultry, pigs, horses, cats and civets.

The first cases of human infection were detected in 2003, in humans exposed to sick birds. The number of WHO confirmed human cases approximately doubled between 2004 and 2005 (46 and 95 respectively), and the number of cases in the first five weeks of 2006 has more than doubled when compared with the average over the same time period in 2005. Based on confirmed cases, the proportion of infected individuals dying has remained at a little over 50% since 2003.[2]

Professor Warwick McKibbin and Dr Alexandra Sidorenko from the Lowy Institute and Australian National University in Australia have estimated that the pandemic might kill 142-million people and wipe about US$4.4-trillion from economic output, according to a worst-case scenario. Even the mild scenario projected loss of 1.4-million lives and close to 0.8% of GDP (approximately US$330 billion) in lost economic output.[3]

The cause of mortality in H5N1 avian influenza infection appears to be primarily from a 'cytokine storm' in the immune system which leads to severe respiratory illness and other complications.[4] This is a condition in which the immune system massively over-responds and becomes imbalanced, resulting in hyper-induction of pro-inflammatory cytokines such as TNF-alpha, IL-1, IL-6, RANTES and interferon-beta and the chemokine IP-10.[5,6,7]

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[1] World Health Organization. *H5N1 avian influenza timeline*, 28 October 2005 (*http://www.who.int/csr/disease/avian_influenza/Timeline_28_10a.pdf*) [last accessed 20 March 2006].

[2] World Health Organization. *Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO*, 6 February 2006 (*http://www.who.int/csr/disease/avian_influenza/country/cases_table_2006_02_06/en/index.html*) [last accessed 20 March 2006].

[3] McKibbin WJ, Sidorenko AA. *Global Macroeconomic Consequences of Pandemic Influenza.* Lowy Institute for International Policy Report, Lowy Institute, Sydney. 79 pp. (*http://www.lowyinstitute.org/Publication.asp?pid=345*) [last accessed 20 March 2006].

[4] Beigel JH, Farrar J, Han AM, Hayden FG, Hyer R, de Jong MD, Lochindarat S, Nguyen TK, Nguyen TH, Tran TH, Nicoll A, Touch S, Yuen KY; Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5. Avian influenza A (H5N1) infection in humans. *New England Journal Medicine*, 2005; 353(13): 1374-85. Review.

[5] Cheung CY, Poon LL, Lau AS, Luk W, Lau YL, Shortridge KF, Gordon S, Guan Y, Peiris JS. Induction of proinflammatory cytokines in human macrophages by influenza A (H5N1)

Exacerbating matters, lethal H5N1 influenza viruses, unlike other human, avian and swine influenza viruses, appear to be resistant to the antiviral effects of interferons and TNF-alpha.[8,9]

However, the recent isolation of the virus in extra-pulmonary sites, as well as a wide diversity of symptoms evident in lethal cases,[10] suggests other mechanisms may also be active.[11]

While it is likely that mortality associated with the to-be pandemic strain of H5N1 will be substantially less than 50%, loss of life, morbidity, economic as well as social disruption, are likely to occur globally at levels unprecedented in recent history.[12]

2.2 Limitations of pharmaceutical interventions

The key pharmaceutical interventions that are being developed to help mitigate against a highly pathogenic avian influenza A (HPAI) pandemic are vaccines and anti-viral drugs. Immunity can only be achieved by previous exposure to the specific HPAI viral type or by vaccination, while antiviral drugs aim to reduce morbidity and mortality of infected individuals, although in some cases they may be able to be used prophylactically, but usually only for short periods owing to untoward side effects.

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viruses: a mechanism for the unusual severity of human disease? *Lancet*, 2002; 360(9348): 1831-7.

[6] Chan MCW, Cheung CY, Chui WH, Tsao SW, Nicholls JM, Chan YO, Chan RWY, Long HT, Poon LLM, Guan Y, Peiris JSM. Proinflammatory cytokine responses induced by influenza A (H5N1) viruses in primary human alveolar and bronchial epithelial cells. *Respiratory Research,* 2005, 6:135 [electronic pre-publication version, *http://respiratory-research.com/content/6/1/135*].

[7] Tumpey TM, Garcia-Sastre A, Taubenberger JK, Palese P, Swayne DE, Pantin-Jackwood MJ, Schultz-Cherry S, Solorzano A, Van Rooijen N, Katz JM, Basler CF. Pathogenicity of influenza viruses with genes from the 1918 pandemic virus: Functional roles of alveolar macrophages and neutrophils in limiting virus replication and mortality in mice. *Journal of Virology*, 2005; 79 (23): 14933-14944.

[8] Seo SH, Hoffmann E, Webster RG. Lethal H5N1 influenza viruses escape host anti-viral cytokine responses. Nature Medicine, 2002; 8(9): 950-4. Epub 2002 Aug 26.

[9] Seo SH, Hoffmann E, Webster RG. The NS1 gene of H5N1 influenza viruses circumvents the host anti-viral cytokine responses. *Virus Research*, 2004; 103(1-2): 107-13.

[10] Chotpitayasunondh T, Ungchusak K, Hanshaoworakul W, Chunsuthiwat S, Sawanpanyalert P, Kijphati R, Lochindarat S, Srisan P, Suwan P, Osotthanakorn Y, Anantasetagoon T, Kanjanawasri S, Tanupattarachai S, Weerakul J, Chaiwirattana R, Maneerattanaporn M, Poolsavathitikool R, Chokephaibulkit K, Apisarnthanarak A, Dowell SF. Human disease from influenza A (H5N1), Thailand, 2004. *Emerging Infectious Diseases*, 2005; 11(2): 201-9.

[11] Wong SSY, Yuen K, Avian influenza virus infections in humans. *Chest*, 129 (1): 156-168.

[12] World Health Organization. *Avian influenza: assessing the pandemic threat*. 2005. WHO, Geneva. 62 pp.

2.2.1 Vaccine limitations

These are numerous and have been well reported. They include:

- Vaccine manufacture cannot be commenced until a pandemic strain is identified[12]
- Multiple strains of HPAI virus may co-exist requiring multiple vaccines[13]
- Vaccines, to remain effective, will need to map the 'moving target' of a mutating pandemic strain or, more difficult still, multiple strains[3]
- Two vaccinations per person may be required in order to acquire immunity against HPAI[14]
- Vaccine manufacture is concentrated in nine countries worldwide causing distribution challenges[3]
- Vaccine manufacturing capacity is limited and is unlikely to be able to cater in the short-term for the majority of the world's population.[15]

2.2.2 Antiviral drug limitations

The principal limitations that may result from proposed wide-scale use of antiviral drugs to help reduce mortality and morbidity in the event of a pandemic include:

- Viral resistance may develop rapidly to any drug used on a wide scale[16]
- As of January 2006, 16% of cases of human infection with H5N1 had a viral type with oseltamivir (Tamiflu®) resistance[17]

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[13] Fedson DS. Preparing for pandemic vaccination: an international policy agenda for vaccine development. *Journal of Public Health Policy*, 2005; 26(1): 4-29.

[14] Enserink M (2005) Avian influenza: 'Pandemic vaccine' appears to protect only at high doses. *Science*, 309: 996.

[15] Secretariat, World Health Organization. *Strengthening pandemic influenza preparedness and response*. Report to the 58th World Health Assembly, Ref A58/13, 7 April 2005. World Health Organization, Geneva. 7 pp. (*http://www.who.int/csr/disease/influenza/A58_13-en.pdf*) [last accessed 20 March 2006].

[16] Pillay D, Zambon M. Antiviral drug resistance. *British Medical Journal*, 1998; 317(7159): 660-2. Review.

[17] Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. *Lancet Early Online Publication*, 19 January 2006.

- There are supply and cost constraints over providing the world's population with antiviral drugs such as neuraminidinase inhibitors (e.g. oseltamivir and zanamivir [Relenza®])[18,19]

- Efficacy varies between different neuraminidinase and M2 inhibitors (e.g. NA inhibitors: oseltamivir, zanamivir; M2 inhibitors: amantadine, rimantadine), with the latter considered to be generally less effective[20]

- There is very limited clinical evidence to demonstrate that members of either product group will substantially reduce mortality or morbidity, although greatest efficacy is likely if antiviral medications are administered very early in the clinical progression of the disease, i.e. within 48 h of infection[21,22]

- Most western countries are facing considerable challenges to ensure even 25% of their populations will be able to access antiviral drug treatments within the next year[23,24]

- Most antiviral drugs cannot be used prophylactically owing to negative side effects. Some potential candidate anti-virals such as ribavirin typically cause considerably greater negative side effects than oseltamivir[25]

- Resistance to amantadine and rimantidine (M2 inhibitors commonly used against influenza) is already considered to be widespread, but research is required to determine whether combinations of M2 inhibitors and neuraminidinase inhibitors may prove more effective than either drug type singly[26]

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[18] Stiver G. The treatment of influenza with antiviral drugs. *Canadian Medical Association Journal*, 2003; 168(1): 49-56. Review.

[19] Hayden FG. Pandemic influenza: is an antiviral response realistic? *Pediatric Infectious Diseases Journal*, 2004; 3(11 Suppl): S262-9. Review.

[20] Gubareva LV, Kaiser L, Hayden FG. Influenza virus neuraminidase inhibitors. *Lancet*, 2000; 355(9206): 827-35. Review.

[21] Winquist AG, Fukuda K, Bridges CB, Cox NJ. Neuraminidase inhibitors for treatment of Influenza A and B infections. *Morbity and Mortality Weekly Report*, 1999; 48(RR14): 1-9.

[22] Yuen KY, Wong SS. Human infection by avian influenza A H5N1. *Hong Kong Medical Journal*, 2005; 11(3): 189-99. Review.

[23] Monto AS. Vaccines and antiviral drugs in pandemic preparedness. *Emerging Infectious Diseases Journal*, 2006; 12(1): 55-60.

[24] Brooks MJ, Sasadeusz JJ, Tannock GA. Antiviral chemotherapeutic agents against respiratory viruses: where are we now and what's in the pipeline? *Current Opinion Pulmonary Medicine*, 2004; 10(3): 197-203. Review.

[25] Govorkova EA, Fang HB, Tan M, Webster RG. Neuraminidase inhibitor-rimantadine combinations exert additive and synergistic anti-influenza virus effects in MDCK cells. *Antimicrobial Agents and Chemotherapy*, 2004; 48(12): 4855-63.

[26] Le QM, Kiso M, Someya K, Sakai YT, Nguyen TH, Nguyen KH, Pham ND, Ngyen HH, Yamada S, Muramoto Y, Horimoto T, Takada A, Goto H, Suzuki T, Suzuki Y, Kawaoka Y. Avian flu: isolation of drug-resistant H5N1 virus. *Nature*, 2005; 437(7062): 1108.

- Medications are generally taken for treatment rather than prevention of disease, and are expensive by comparison with food, nutrient-based or lifestyle interventions known to help support the immune system against viral infection. [19,27]

2.3 THE POTENTIAL ROLE OF NATURAL PRODUCTS IN A PANDEMIC

Given the challenges posed by adequate supply of effective vaccines and antiviral drugs, the role of non-pharmaceutical interventions as a means of helping to support the immune system must be considered as a matter of priority.

There is ample evidence that human immuno-competence is related to nutrition,[28,29] physical exercise[30] and psycho-social stress.[31]

Accordingly, evidence-based advice and recommendations should be provided to the general public as to nutritional and lifestyle-based methods that can be employed to assist the function of the immune system prior to and during a pandemic.

The fact that nutritional patterns and lifestyles are likely to be altered dramatically during a pandemic is also of critical importance. Food quality, for example, is likely to deteriorate as a result of constraints on the supply of fresh foods. Therefore, interventions such as nutrient supplementation are likely to become even more beneficial as a means of countering micronutrient deficiencies compared with in non-pandemic situations. Such interventions are likely to be cost-effective and their cost may in many cases be borne by individuals rather than governments. Natural health products are widely available, are utilized by large sectors of the population both in the developed and less developed world,[32] do not require prescriptions and may often be used prophylactically.

In the event of an HPAI pandemic, given that some natural products may be harmful at excessive dosage, and that others, such as particular botanical products, may exacerbate the cytokine storm instigated by H5N1 infection, it is considered of paramount importance that recommendations for natural product

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[27] Moscona A. Neuraminidase inhibitors for influenza. *New England Journal Medicine*, 2005; 353(13): 1363-73. Review.

[28] Dreizen S. Nutrition and the immune response - a review. *International Journal for Vitamin and Nutrition Research,* 1979; 49(2): 220-8. Review.

[29] Meydani A, Ahmed T, Meydani SN. Aging, nutritional status, and infection in the developing world. *Nutrition Reviews*, 2005; 63(7): 233-46. Review.

[30] Gani F, Passalacqua G, Senna G, Mosca Frezet M. Sport, immune system and respiratory infections. *Allergie et Immunologie (Paris)*, 2003; 35(2): 41-6. Review.

[31] Elenkov IJ, Chrousos GP. Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. *Annals of the New York Academy of Sciences*. 2002; 966: 290-303. Review.

[32] World Health Organization webpage on "Traditional medicine": *http://www.who.int/mediacentre/factsheets/fs134/en/* [last accessed 20 March 2006].

use are made and adopted by leading health authorities such as the World Health Organization and national health authorities.

Section 3 of this report considers the criteria by which natural products have been selected for consideration in this report, while Section 4 focuses primarily on the evidence base for supplementary use of specific micronutrients and herbal products as a means of supporting the immune system prior to or during viral infection.

Conclusions and Recommendations are offered in Section 7 of this report.

3. NATURAL PRODUCT SELECTION CRITERIA

Although there are a very large number of micronutrients and botanical products that have been demonstrated either via *in vitro* or *in vivo* studies, or through human clinical trials, to have an impact on the immune system, there are relatively few that are likely to have significant impacts on reducing mortality or morbidity following HPAI viral infection.

This is largely owing to the unusual pathogenesis of the disease in humans as well its very rapid clinical progression (see various references in Section 2.1).

Furthermore, it is possible that certain products, notably certain botanicals, which cause a generalised increase in pro-inflammatory cytokines in the cell-mediated (adaptive) immune system could actually exacerbate the cytokine storm following HPAI infection.

Given that it is probable that the time prior to the initiation of a HPAI pandemic is very limited, there is unlikely to be sufficient time for evaluation of large numbers of natural products with respect to their potential for use as mitigating agents. It is pertinent, in the present case, to report on those relatively few products for which there is the greatest likelihood of benefit, based on existing evidence.

As a result, the ANH Avian Influenza Expert Committee has utilized a fairly strict requirement for eligibility of products (generic or proprietary) for this review.

The eligibility requirements utilised are as follows:

a) evidence of *in vitro* and/or *in vivo* studies involving direct challenges with H5N1 virus; and/or,

b) evidence of efficacy in human studies with severe respiratory infections e.g., influenza or viral pneumonia; and,

c) substantial clinical evidence of efficacy in cases of severe respiratory illness; and,

d) Evidence of safety, or at least no evidence of significant harmfulness at dosages proposed.

The ANH Avian Influenza Expert Committee accepts that the nutrients and natural products included in this report do not represent a complete listing of all possible natural prophylactic or therapeutic agents which may have the potential to reduce mortality or morbidity associated with HPAI. The Committee is keen to view and consider evidence relating to other natural products in due course.

4. KEY MICRONUTRIENTS

This section of the report provides scientific evidence and justification for the proposed use of specific micronutrients in the event of an HPAI H5N1 pandemic.

4.1 ZINC

4.1.1 Proposed mechanisms of action on the immune system

The role of zinc as a critical element in the functioning of the immune system of mammals including humans has been known since the mid-1970s.[33,34]

However, more recently, research has demonstrated that zinc's key mechanism of action in the immune system is by stimulating serum thymulin (a thymus specific hormone involved in T cell function)[35] and modulation of T helper cell functions (correction of Th1/Th2 imbalance in zinc deficiency).[36,37] Additionally, in zinc deficient subjects, lytic activity of natural killer cells and the percentage of precursors of cytolytic T cells is decreased.[38] Three key papers which elucidate these mechanisms are summarized below:

Beck et al (1997)[26] showed clearly that mild zinc deficiency in humans (n=5) led to an imbalance between the production of cytokines from Th-1 and Th-2 cells. This was demonstrated by the significantly reduced production of IF-γ cytokines (produced by Th-1 cells) following zinc depletion, whereas production of IL-4, IL-6 and IL-10 cytokines (produced by Th-2 cells) was unaffected. The study also showed borderline statistical significance in the reduction of IL-1 (produced by macrophages, in turn originating in bone marrow) in zinc-deficient subjects. (Elevated production of IL-1 cytokines produce the typical flu symptoms). The same study also showed that this imbalance in cytokine response between Th-1 and Th-2 cells resulted in significantly decreased recruitment of T naïve cells (CD4+CD45RA), as well as CD73+ cells in the CD8+ subset which are precursors to cytotoxic T lymphocytes (CTL). Levels of cytokines and T cells returned to baseline following zinc repletion.

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[33] Moynahan EJ. Letter: Zinc deficiency and cellular immune deficiency in acrodermatitis enteropathica in man and zinc deficiency with thymic hypoplasia in fresian calves: a possible genetic link. *Lancet*, 1975; 2(7937): 710.

[34] Moynahan EJ. Acrodermatitis enteropathica in two siblings treated with zinc sulphate supplements alone. *Proceedings of the Royal Society of Medicine*, 1975; 68(5): 276.

[35] Prasad AS, Meftah S, Abdallah J, Kaplan J, Brewer GJ, Bach JF, Dardenne M. Serum thymulin in human zinc deficiency. *Journal of Clinical Investigation*, 1988; 82(4): 1202-10.

[36] Prasad AS. Zinc and immunity. *Molecular and Cellular Biochemistry*, 1998; 188(1-2): 63-9. Review.

[37] Shankar AH, Prasad AS. Zinc and immune function: the biological basis of altered resistance to infection. *American Journal of Clinical Nutrition,* 1998; 68(suppl): 447S–63S.

[38] Beck FW, Prasad AS, Kaplan J, Fitzgerald JT, Brewer GJ. Changes in cytokine production and T cell subpopulations in experimentally induced zinc-deficient humans. *American Journal of Physiology,* 1997; 272(6 Pt 1): E1002-7.

Professor Ananda Prasad, a key zinc researcher who was largely responsible for the discovery of the essentiality of zinc in the 1960s, reviewed in 2000[39] the various human studies to have been conducted in his laboratory. Prasad demonstrates how reduction of IF-γ and IL-2 might be key causes of increased susceptibility to infectious diseases in zinc deficient subjects and how such changes in cytokines are associated with reduced production of natural killer (NK) cells and precursors of T lymphocytes. The author shows that intakes of 3-5 mg zinc (approximately 50% of the Reference Nutrient Intake) per day over 20 weeks induced mild zinc deficiency which compromised immune function. He also comments that mild zinc deficiency is widespread even in developed countries and stresses that plasma zinc is not a good method of assessing zinc status where deficiency is mild. Atomic absorption analysis of zinc in lymphocytes, granulocytes and platelets is a much better and more sensitive method (as per Beck *et al*. 1997).[38]

Prasad *et al*. (2002)[40] demonstrated for the first time the likely mechanism of T cell activation and proliferation by IL-2. They showed in human cell lines that zinc is required for the gene expression of IL-2 and it's receptors in T cells, partly as a result of decreased activation of the transcription factor NF-KappaB, which is in turn triggered by TNF-alpha (see excellent study by Bouwmeester *et al.* 2004).[41] This shows that zinc effectively facilitates the binding of IL-2 to IL-2 receptors in T cells.

Other mechanisms of zinc's action on the human system have been discussed in a useful review by Sprietsma (1999).[42] It is proposed that there are interactions between zinc ions, glutathione, and nitric monoxide, which can correct premature transition from efficient Th-1-dependent cellular antiviral immune functions to Th-2-dependent humoral immune functions, as well as stimulating specific enzymes.

It is well known that zinc is an essential nutrient in terms of immune system function, and that deficiencies result in compromised immune function.[43] Furthermore, although the precise mechanism of zinc's action has not been fully defined, there is good evidence that zinc salts can potentiate 10-fold the anti-viral

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[39] Prasad AS. Effects of zinc deficiency on Th1 and Th2 cytokine shifts. *Journal of Infectious Diseases,* 2000; 182 Suppl 1: S62-8.

[40] Prasad AS, Bao B, Beck FW, Sarkar FH. Zinc enhances the expression of interleukin-2 and interleukin-2 receptors in HUT-78 cells by way of NF-kappaB activation. *J Lab Clin Med.*, 2002; 140(4): 272-89.

[41] Bouwmeester T, Bauch A, Ruffner H, Angrand PO, Bergamini G, Croughton K, Cruciat C, Eberhard D, Gagneur J, Ghidelli S, Hopf C, Huhse B, Mangano R, Michon AM, Schirle M, Schlegl J, Schwab M, Stein MA, Bauer A, Casari G, Drewes G, Gavin AC, Jackson DB, Joberty G, Neubauer G, Rick J, Kuster B, Superti-Furga G. A physical and functional map of the human TNF-alpha/NF-kappa B signal transduction pathway. *Nat Cell Biol*. 2004, 6 (2): 97-105.

[42] Sprietsma JE. Modern diets and diseases: NO-zinc balance. Under Th1, zinc and nitrogen monoxide (NO) collectively protect against viruses, AIDS, autoimmunity, diabetes, allergies, asthma, infectious diseases, atherosclerosis and cancer. *Medical Hypotheses*, 1999; 53(1): 6-16. Review.

[43] Ibs KH, Rink L. Zinc-altered immune function. *Journal of Nutrition*, 2003; 133 (5 Suppl 1): 1452S-6S.

action of the human cytokine interferon-alpha.[44] It has also been shown in a mouse model that zinc is an essential component of specific superoxide dismutase enzymes, which can significantly reduce mortality rates and virus titers following Influenza A infection.[45] The adverse effects of a zinc deficiency include, but are not limited to, an increased severity and duration of viral and other infections,[46] poor immune system modulation,[47] as well as an increased propensity of lung epithelia and airways to become inflamed.[48] Correction of a zinc deficiency rapidly restores normal immune system function and modulation.[49,50,51 ,52]

Zinc deficiencies are widespread across the globe,[53] and may result from a combination of factors including low zinc status in foods caused by mineral depletion of agricultural soils,[54,55] dietary changes leading to reduced consumption

[44] Berg K, Bolt G, Andersen H, Owen TC. Zinc potentiates the antiviral action of human IFN-alpha tenfold. *Journal of Interferon Cytokine Research*, 2001; 21(7): 471-4.

[45] Serkedjieva J, Roeva I, Angelova M, Dolashka P, Voelter WG. Combined protective effect of a fungal Cu/Zn-containing superoxide dismutase and rimantadine hydrochloride in experimental murine Influenza A virus infection. *Acta Virologica,* 2003; 4 (1): 53-6.

[46] Beck FW, Prasad AS, Kaplan J, Fitzgerald JT, Brewer GJ. Changes in cytokine production and T cell subpopulations in experimentally induced zinc-deficient humans. *American Journal of Physiology,* 1997; 272 (6 Pt 1): E1002-7.

[47] Rink L, Gabriel P. Extracellular and immunological actions of zinc. *Biometals*, 2001; 14(3-4): 367-83.

[48] Truong-Tran AQ, Carter J, Ruffin R, Zalewski PD. New insights into the role of zinc in the respiratory epithelium. *Immunology and Cell Biology*, 2001; 79(2): 170-7.

[49] Ruel MT, Rivera JA, Santizo MC, Lonnerdal B, Brown KH. Impact of zinc supplementation on morbidity from diarrhea and respiratory infections among rural Guatemalan children. *Pediatrics*. 1997; 99(6): 808-13.

[50] Sazawal S, Black R, Jalla S, Mazumdar S, Sinha A, Bhan MK. Zinc supplementation reduces the incidence of acute lower respiratory infections in infants and preschool children: a double blind controlled trials. *Pediatrics* 1998; 102: 1–5.

[51] Prasad AS, Fitzgerald JT, Bao B, Beck FW, Chandrasekar PH. Duration of symptoms and plasma cytokine levels in patients with the common cold treated with zinc acetate. A randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine*, 2000; 133(4): 245-52.

[52] Mocchegiani E, Muzzioli M. Therapeutic application of zinc in human immunodeficiency virus against opportunistic infections. *Journal of Nutrition*, 2000; 130 (5S Suppl): 1424S-31S.

[53] Prasad AS. Zinc deficiency in humans: a neglected problem. *Journal of the American College of Nutrition*, 1998; 17(6): 542-3. Editorial.

[54] Welch RM (2001). In: *Perspectives on the Micronutrient Nutrition of Crops* (Eds Singh K, Mori S, Welch RM). Scientific Publishers, Jodhpur, India. 294 pp.

[55] Thomas D. A study on the mineral depletion of the foods available to us as a nation over the period 1940 to 1991. *Nutrition and Health*, 2003; 17(2): 85-115.

of red meats,[56] and increased consumption of cereals high in phytates which reduce significantly zinc absorption from the gastrointestinal tract.[57] In the UK alone, 100% of women and 93% of men fail to achieve the UK label Recommended Daily Allowance (RDA) for zinc (15 mg /day),[58] an amount that is at least 60% below that required for optimal immune system function.[43]

4.1.2 Human zinc requirements

The plasma pool of zinc is very low (normal range: 12-16µmol/L) but is highly mobile and critically important to immune function.[59,60] Most of the zinc in serum is bound to proteins and other ligands.[61] Additionally, the Daily Reference Intake (DRI) has been based by the US Institute of Medicine (IoM) on an apparent regression between absorbed and ingested zinc, albeit on limited data.[62] From these data, derived from Hunt *et al*. (1992)[63], Jackson *et al.* (1984)[64], Lee *et al.* (1993)[65], Taylor *et al.* (1991)[66], Turnlund *et al.* (1984[67], 1986[68]), Wada *et al.*

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[56] Richardson NJ. UK consumer perceptions of meat. *Proceedings of the Nutrition Society*, 1994; 53; 281-287.

[57] Lonnerdal B. Dietary factors influencing zinc absorption. *Journal of Nutrition*, 2000; 130 (5S Suppl): 1378S-83S.

[58] Food Standards Agency. *The National Diet & Nutrition Survey: adults aged 19 to 64 years. Vitamin and mineral intakes and urinary analytes*. Vol 3, 2003; 160 pp.

[59] Favier A & Favier M. Consequences des de .cits en zinc durant la grossesse pour la mere et le nouveau ne. *Rev.Fr.Gynecology and Obstetrics*, 1990; 85: 13 –27.

[60] Ibs K-H, Rink L. Zinc altered immune function. *Journal of Nutrition*, 2003; 133: 1452S-1456S.

[61] Scott BJ Bradwell AR. Identication of the serum binding proteins for iron, zinc, cadmium, nickel and calcium. *Clinical.Chemistry*, 1983; 29: 629 –633.

[62] Institute of Medicine (2000). *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Food and Nutrition Board (FNB), Institute of Medicine (IOM), USA. (*http://www.nap.edu/books/0309072794/html/450.html*)

[63] Hunt JR, Matthys LA, Johnson LK. Zinc absorption, mineral balance, and blood lipids in women consuming controlled lactoovovegetarian and omnivorous diets for 8 wk. *American Journal of Clinical Nutrition*, 1998; 67(3): 421-30.

[64] Jackson MJ, Jones DA, Edwards RH, Swainbank IG, Coleman ML. Zinc homeostasis in man: studies using a new stable isotope-dilution technique. *British Journal of Nutrition*, 1984; 51(2): 199-208.

[65] Lee DY, Prasad AS, Hydrick-Adair C, Brewer G, Johnson PE. Homeostasis of zinc in marginal human zinc deficiency: role of absorption and endogenous excretion of zinc. *Journal of Laboratory and Clinical Medicine*, 1993; 122(5): 549-56.

[66] Taylor CM, Bacon JR, Aggett PJ, Bremner I. Homeostatic regulation of zinc absorption and endogenous losses in zinc-deprived men. *American Journal of Clinical Nutrition*, 1991; 53(3):755-63. Erratum in: *Amercan Journal of Clinical Nutrition*, 1992; 56(2): 462.

[67] Turnlund JR, King JC, Keyes WR, Gong B, Michel MC. A stable isotope study of zinc absorption in young men: effects of phytate and alpha-cellulose. *American Journal of Clinical Nutrition*, 1984; 40(5): 1071-7.

(1985)[69], the key characteristics of the 'best' asymptotic fitted absorption curve are:

a) the rapid absorption rates at low intake levels, and;
b) subsequent reduced absorption rates approaching apparent saturation at higher levels of intake, in the 12-17 mg/day range. Based on the fitted curve, absorption of zinc at intake levels greater than 10 mg/day would appear negligible.

There are a number of problems associated with the interpretations made for the DRI, these being summarised below:

- The apparent asymptotic 'fitted' curve does not appear to accurately reflect the data, and given the absence of dosages greater than 17 mg/day, it is not possible to imply that higher dosages are not physiologically beneficial

- Sufficiency of Zn has been determined on the basis of the relationship between exogenous and endogenous zinc as determined via zinc in serum or plasma, when such values have elsewhere been shown to be poor indicators of zinc status, particularly in cases of mild zinc deficiency, where immune function remains compromised[38,39,70]

- The determinations relating to zinc homeostasis used in the DRI assessment by the IoM have been based largely on the addition of radio-labelled zinc to diets, yet the absorption of dietary zinc is known to be poor, particularly when consumed as part of a phytate-rich diet.[57] In terms of dietary sources, it is well established that zinc absorption from meats tends to be greatest, while that from plant sources, especially phytate-rich cereals, is poorer.[71] Delivery of zinc ions via zinc lozenges dissolved in the buccal activity or via a supplemental solution given orally on an empty stomach may give significantly different results, as might delivery of higher dosages. Given there has been a significant trend among the general population, particularly in developed countries, away from red meat-eating (see Richardson 1994, and UK Vegetarian Society data[72]), the average absorption rate of zinc could have declined

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[68] Turnlund JR, Durkin N, Costa F, Margen S. Stable isotope studies of zinc absorption and retention in young and elderly men. *Journal of Nutrition*, 1986; 116(7): 1239-47.

[69] Wada L, Turnlund JR, King JC. Zinc utilization in young men fed adequate and low zinc intakes. *Journal of Nutrition*, 1985; 115(10): 1345-54.

[70] Agte VV, Chiplonkar SA, Tarwadi KV. Factors influencing zinc status of apparently healthy Indians. *Journal of the American College of Nutrition*, 2005; 24(5): 334-41.

[71] Hunt JR, Matthys LA, Johnson LK. Zinc absorption, mineral balance, and blood lipids in women consuming controlled lactoovovegetarian and omnivorous diets for 8 wk. *American Journal of Clinical Nutrition*, 1998; 67(3): 421-30.

[72] Richardson NJ. UK consumer perceptions of meat. *Proc Nutrition Soc*, 1994; 53; 281-287. Additionally data from the UK Vegetarian Society show that ca. 7% of the adult population and 12% of young people are fully vegetarian, while 41% of the population are "*including far less meat in their diet….. In the UK alone, approximately five thousand people each week are choosing to give meat a miss and join the veggie revolution. If such*

considerably compared with intakes determined decades ago when the average diet contained a significantly greater meat content. Additionally, where zinc intake is from supplements, it should be noted that mineral supplements are most commonly taken in conjunction with meals. This would undoubtedly reduce the availability of free zinc ions, particularly when phytates are abundant. A study undertaken by the UK Food Standards Agency confirmed that zinc intakes were generally low but also showed that zinc bioavailability was lowest in a poultry/fish-based diet compared with a red meat-based diet and a lacto-ovo-vegetarian diet.[73] Interestingly, zinc present in drinking water may be more bioavailable, but levels in most drinking waters are low and have been considered as a component of the 'all sources' intake determined during the UK National Diet and Nutrition Survey[74]

- Confidence in the data derived from zinc intakes exceeding 12 mg /day appears to be poor (note wide spread of data), and the apparent asymptote may, at least to a degree, be an artefact of the limited data used. It is known that higher intakes can raise plasma levels of zinc substantially above 30 µmol Zn/L[60]

- None of the data cited in the DRI relate to the amounts or forms of zinc required to modulate the human immune system.

Based on the above data, the authors of this report argue that the DRI for zinc should be revisited as a matter of urgency, particularly in view of the risk of a HPAI pandemic. In addition, the efficacy and safety of different forms of zinc should be determined, given differences in bioavailability of zinc ions between different formulations. The UK Expert Group on Vitamins and Minerals has determined a Safe Upper Level for oral intake of zinc of 25 mg / day,[75] but this is considered by this Expert Committee as an underestimate for many forms of the nutrient, particularly liquid, ionic forms (as in the case of silver, where salts are generally considerably more toxic than free ions; see Section 4.5 of this report).

It seems likely, from available data and clinical practice, that in most adults, supplemental intake of bioavailable forms of zinc, in the region of 25-50 mg Zn/day/adult, may help to modulate Th-1/Th-2 cytokine production in the immune system, and to stimulate lytic activity of natural killer cells and T-cell precursors.

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*trends were to continue, it is estimated that by the year 2030 everyone in the UK will be a vegetarian." (*www.vegsoc.org/news/2000/21cv/introduction.html).

[73] Food Standards Agency (2003) *The bioavailability of iron, zinc and copper in meat-containing and vegetarian diets in the UK* (Project N05015), UK. (*www.food.gov.uk/science/research/researchinfo/nutritionresearch/optimalnutrition/n05programme/n05listbio/n05015/*) [last accessed 20 March 2006].

[74] Food Standards Agency. *The National Diet & Nutrition Survey: adults aged 19 to 64 years. Vitamin and mineral intakes and urinary analytes*. Vol 3, 2003; 160 pp.

[75] Expert Group on Vitamins and Minerals [UK] (2003) *Safe upper levels for vitamins and minerals*. Report of the Expert Group on Vitamins and Mineral. Food Standards Agency, May 2003. ISBN 1-904026-11-7. [Available at http://www.food.gov.uk/multimedia/pdfs/vitamin2003.pdf]

4.1.3 Prevention

Zinc supplementation has been clearly demonstrated to reduce the effects of respiratory illness, as well as other infectious diseases including diarrhoea.

Sazawal *et al.* (1998)[76] demonstrated in a randomised, double-blind, controlled study in India (zinc, n = 298; control, n = 311) that when preschool children aged 6 to 35 months were given 10 mg Zn per day over 6 months (except in cases of diarrhoeal disease when intakes were doubled to counteract faecal loss), the rate of respiratory infections, principally pneumonia, was reduced by around 45% compared with the placebo group. This effect occurred over and above the effects of antibiotics which were freely available to and used by children suffering respiratory and diarrhoeal illness.

For a 6 month child of 7.5 kg body weight and a 36-month child of 14 kg body weight, a 10 mg Zn dosage equates to the equivalent of 80 mg and 43 mg doses respectively for a 60 kg adult.

In another study community-based, randomised, double-blind, controlled study conducted by Ruel *et al.*[77] in Guatemala (zinc, n = 45; control, n = 44), respiratory infections were reduced by 22% and persistent diarrhoeal episodes by 67% compared with the control group.

4.1.4 Treatment

Prasad *et al.* (2000) determined duration of cold symptoms in zinc-treated (n = 25) and placebo-treated (n = 23) subjects. Zinc was delivered as zinc ions from zinc acetate in lozenges to enhance buccal absorption (intestinal absorption is known to be poor). The authors found that the zinc lozenges reduced the severity of symptoms and duration of colds, and moderated proinflammatory cytokines (notably IL-1) which cause classic cold and flu symptoms. The authors cite five other studies investigating the effects of zinc lozenges (all these trials were conducted with zinc gluconate) and they failed to show beneficial effects against colds. The authors suggest that perhaps the dosages were too low or the form of zinc prevented release of sufficient bioavailable zinc (ions).[39,50]

A study on evaluating the efficacy of a commercially available zinc nasal gel (Zicam®) following recent onset of common cold (< 24 h from start of symptoms) was conducted over 5 months at four different centres in the USA (zinc, n = 108; control, n = 105).[78] The authors found that the duration of symptoms was 2.3 days (+/-0.9) in the zinc group and 9.0 days (+/-2.5) in the control group. However, a separate paper describes severe hyposmia or anosmia (loss of sense of smell) following treatments with zinc nasal spray, which may be long lasting.

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[76] Sazawal S, Black RE, Jalla S, Mazumdar S, Sinha A, Bhan MK. Zinc supplementation reduces the incidence of acute lower respiratory infections in infants and preschool children: a double-blind, controlled trial. *Pediatrics*, 1998; 102(1 Pt 1): 1-5.

[77] Ruel MT, Rivera JA, Santizo MC, Lonnerdal B, Brown KH. Impact of zinc supplementation on morbidity from diarrhea and respiratory infections among rural Guatemalan children. *Pediatrics*. 1997; 99(6): 808-13.

[78] Hirt M, Nobel S, Barron E. Zinc nasal gel for the treatment of common cold symptoms: a double-blind, placebo-controlled trial. *Ear Nose Throat Journal*, 2000; 79(10): 778-80, 782.

This effect, considered to be relatively dose insensitive, was attributed to a direct effect of zinc ions on the highly sensitive nasal mucosa[79] and has subsequently been the subject of court cases. Oral supplementation in the ≤ 50 mg Zn / day range has not been associated with any toxicity response of this type.

Note: the authors of this report are aware of specific *in vitro* and *in vivo* studies that have been undertaken since October 2005 by major, independent research facilities in both the UK and the USA, regarding a proprietary (patented) liquid zinc supplement and challenges with the H5N1 virus. Further studies are underway at the time of writing. These studies have demonstrated considerable potential for the use of at least one form of supplementary zinc.

[79] Jafek BW, Linschoten MR, Murrow BW. Anosmia after intranasal zinc gluconate use. *American Journal of Rhinology*, 2004; 18(3): 137-41.

4.2 VITAMIN C

The role of vitamin C (ascorbic acid, ascorbate) in fighting infectious diseases became well known and controversial with the publication of Dr Linus Pauling's book on the common cold.[80] Pauling reviewed substantial suggestive evidence on the efficacy of large doses for the treatment and prevention of viral diseases. Since then, apparently ambiguous evidence has been presented, leading to scientific and medical controversy.

Recently, a rigorous analysis of the data has shown that all the available scientific evidence is consistent with the hypothesis that *large* doses of vitamin C provide a highly effective treatment.[81] Some of the evidence for this new viewpoint is summarized here.

4.2.1 Pharmacological actions

Ascorbate acts as a redox cycling antioxidant, and all established physiological functions of ascorbate involve donation or acceptance of electrons. Ascorbate can reduce most relevant reactive oxygen species within the body.[82,83] It readily quenches reactive oxygen and nitrogen species, including hydroxyl, peroxyl, superoxide, peroxynitrite, nitroxide radicals, singlet oxygen and hypochlorite.[84,85] The vitamin functions as a cofactor for enzyme reactions, which often involve a reduced divalent metalloenzyme. It also functions as an intracellular and extracellular antioxidant in the aqueous phase.[86,87,88] *In vivo*, ascorbate is rapidly regenerated from its oxidized forms, dehydroascorbate and the ascorbyl radical, by several NADPH dependent enzymes, glutathione and NAD.[89,90] Vitamin C is

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[80] Pauling L. (1970) *Vitamin C and the common cold*. WH Freeman: New York.

[81] Hickey S, Roberts H J, Cathcart RF. Dynamic flow: a new model for ascorbate. *Journal of Orthomolecular Medicine*, 2006 [in press].

[82] Buettner GR. The pecking order of free radicals and antioxidants, Lipid peroxidation, a-tocopherol, and ascorbate. *Archives of Biochemistry and Biophysics*, 1993; 300: 535-543.

[83] Bors W, Buettner GR. (1997) *The vitamin C radical and its reactions*, in Vitamin C in Health and Disease, Ed. by L. Packer and J. Fuchs. Marcel Dekker: New York, 75-94.

[84] Frei B, England L, Ames BN. Ascorbate is an outstanding antioxidant in human blood plasma. *Proceedings of National Academy of Science*, 1989; 86: 6377–6381.

[85] Sies H, Stahl W. Vitamins E and C, beta-carotene, and other carotenoids as antioxidants. *American Journal of Clinical Nutrition*, 1995; 62: 1315S–1321S.

[86] Englard S, Seifter S. *The biochemical functions of ascorbic acid. Annual Review of Nutrition*, 1986; 6: 365–406.

[87] Tsao CS. (1997) *An overview of ascorbic acid chemistry and biochemistry*. In: Packer L, Fuchs J, eds. Vitamin C in Health and Disease. New York: Marcel Dekker.

[88] Halliwell B, Whiteman M. (1997) *Antioxidant and prooxidant properties of vitamin C*. In: Packer L, Fuchs J, eds. Vitamin C in Health and Disease. New York: Marcel Dekker.

[89] Park JB, Levine M. Purification, cloning and expression of dehydroascorbic acid-reducing activity from human neutrophils: Identification as glutaredoxin. *The Biochemical Journal*, 1996; 315: 931–938.

known to be an electron donor for many human enzymes and numerous roles, including its involvement in collagen hydroxylation and the biosynthesis of hormones, amino acids and carnitine.

Vitamin C has long been claimed to inactivate viruses. To take a recent example, a combination of ascorbate and copper was shown to inactivate herpes simplex, in a murine model. Neither ascorbate nor copper alone inactivated the virus, but the combination, which is known to act as a pro-oxidant, was "completely effective".[91]

The antiviral effects of ascorbate may involve it acting as a pro-oxidant. Such actions have been proposed as possible side effects of high doses. However, increasing evidence suggests that the pro-oxidant action may be beneficial. For example, by inducing selective free radical damage, ascorbate induces apoptosis in cancer cells.[92,93] It has a similar antiviral effect.[94] Copper and ascorbate combine in a Fenton reaction, producing hydrogen peroxide and other reactive species, in a redox cycle. In healthy cells, the effects of futile redox cycling are inhibited by catalase and peroxidase.[95] However, virally infected tissues and cancer are less able to combat the oxidative effects of these reations.[93,94]

Vitamin C is known to inhibit inflammation and reduce shock. Ascorbate is involved in the synthesis of catecholamines and protects them against oxidation.[96,97,98] In conditions of shock, vitamin C has a direct protective action on

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[90] May JM, Cobb CE, Mendiratta S, Hill KE, Burk RF. Reduction of the ascorbyl free radical to ascorbate by thioredoxin reductase. *The Journal of Biological Chemistry*, 1998; 273: 23039–23045.

[91] Betanzos-Cabrera G, Ramirez FJ, Munoz JL, Barron BL, Maldonado R. Inactivation of HSV-2 by ascorbate-Cu(II) and its protecting evaluation in CF-1 mice against encephalitis. *Journal of Virological Methods*, 2004; 120(2): 161-165.

[92] Padayatty SJ, Levine M. Reevaluation of Ascorbate in Cancer Treatment: Emerging Evidence, Open Minds and Serendipity. *Journal of the American College of Nutrition*, 2000; Vol. 19 (4): 423-425.

[93] Casciari JJ, Riordan NH, Schmidt TL, Meng XL, Jackson JA, Riordan HD. Cytotoxicity of ascorbate, lipoic acid, and other antioxidants in hollow fibre in vitro tumours. *British Journal of Cancer*, 2001 84(11): 1544-1550.

[94] Chen Q, Espey MG, Krishna MC, Mitchell JB, Corpe CP, Buettner GR, Shacter E, Levine M. Pharmacologic ascorbic acid concentrations selectively kill cancer cells: action as a pro-drug to deliver hydrogen peroxide to tissues. *Proceedings of National Academy of Science*, 2005; 102(38): 13604-13609.

[95] Halliwell B, Gutteridge JMC. (1999)*Free Radicals in Biology and Medicine*. OUP: Oxford, England.

[96] Furchgott R.F. The pharmacology of vascular smooth muscle. *Pharmacol Rev* 1956; 7: 183–265.

[97] Kitto HJ, Bohr DF. Some agents which potentiate the inotropic response of papillary muscle to epinephrine. *American Journal of Physiology*, 1953; 175: 343–348.

[98] Maxwell LC, Herlihy JT, Riedel GL. Effects of ascorbic acid and EDTA on vascular concentration n-response to catecholamines. *Microvascular Research,* 1983; 26: 81–88.

blood vessel tone.[99] This may explain reported beneficial effects of ascorbate against shock, in both animals[100,101,102] and humans.[103] In particular, such a direct pharmacological action may diminish the shock associated with infectious diseases, providing a physiological explanation for the numerous reports of dramatic effects of intravenous sodium ascorbate in severe shock and infection.[104]

4.2.2 Pharmacokinetics of low doses

Vitamin C has a dual phase pharmacokinetic profile. In healthy, young, adult humans, at low doses, the excretion half-life varies widely (from 8 to 40 days) and is inversely related to the ascorbate body pool, because of homeostatic regulation. [105] Vitamin C is actively removed from the gut and at doses below 60 mg, almost all is absorbed.[106] The proportion (though not the absolute amount) absorbed in a healthy individual decreases with dose: up to 80-90% of a 180mg dose is absorbed,[107] this reduces to 75% at 1 gram, 50% at 1.5 grams, 26% at 6 grams and 16% at 12 grams.[108,109,110] The pharmacokinetics of vitamin C in healthy

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[99] Dillon PF, Root-Bernstein RS, Lieder CM. Antioxidant-independent ascorbate enhancement of catecholamine-induced contractions of vascular smooth muscle. *American Journal of Physiology Heart and Circulatory Physiology*, 2004; 286(6): H2353-2360.

[100] Pavlovic S, Fraser R. Effects of different levels of vitamin C intake on the vitamin C concentration in guinea pigs plasma and the effect of vitamin C intake on anaphylaxis. *Medicine Interne*, 1988; 26(3): 235-244.

[101] Feigen GA, Smith BH, Dix CE, Flynn CJ, Peterson NS, Rosenberg LT, Pavlovic S, Leibovitz B. Enhancement of antibody production and protection against systemic anaphylaxis by large doses of vitamin C. *Research Communications in Chemical Pathology and Pharmacology*, 1982; 38(2): 313-33.

[102] Wu F, Wilson JX, Tyml K. Ascorbate inhibits iNOS expression and preserves vasoconstrictor responsiveness in skeletal muscle of septic mice. *American Journal of Physiology - Regulatory Integrative and Comparative Physiology*, 2003; 285(1): R50-6 [electronic pre-publication version, *http://ajpregu.physiology.org/cgi/reprint/00564.2002v1.pdf*].

[103] Galley HF, Howdle PD, Walker BE, Webster NR. The effects of intravenous antioxidants in patients with septic shock. *Free Radical Biology and Medicine*, 1997; 23(5): 768-674.

[104] Levy TE. (2002) *Vitamin C, Infectious Disease and Toxins.* Xlibris: Philadelphia, USA.

[105] Kallner A, Hartmann I, Hornig D. Steady-state turnover and body pool of ascorbic acid in man. *American Journal of Clinical Nutrition*, 1979; 32: 530-539.

[106] Baker E.M, Hodges RE, Hood J, Sauberlich HE, March SC. Metabolism of ascorbic-1-14C acid in experimental human scurvy. *American Journal of Clinical Nutrition*, 1969; 22 (5): 549-558.

[107] Kallner A, Hartmann I, Hornig D. On the absorption of ascorbic acid in man. *International Journal of Vitamin and Nutrition Research*, 1977; 47: 383-388.

[108] *Expert Group on Vitamins and Minerals*, UK government update paper, 1999; EVM/99/21/P.

[109] Hornig DH, Moser U. (1981) *The safety of high vitamin C intakes in man. In: Vitamin C (ascorbic acid).* (Eds. Counsell JN, Hornig DH) Applied Science Publishers: New Jersey.

[110] Kallner A, Hartmann I, Hornig D. On the absorption of ascorbic acid in man. *International Journal of Vitamin and Nutrition Research*, 1977; 47: 383-388.

adults has been extensively studied by Levine *et al.*[111,112] and others.[113] The pharmacokinetics in other groups, such as children or the aged, has not been fully quantified.

4.2.3 Pharmacokinetics of large doses

High doses of vitamin C, producing a blood plasma level above a threshold of about 70 microM/L, have a short excretion half-life: approximately half an hour.[114] Large oral doses give a transient plasma response, with the blood level increasing and then decreasing, with a pulse wavelength of about 5 hours.[111,112,113] In healthy adults, this transient increase has a maximum peak approaching 250 microM/L. This is consistent with the reduced absorption rate of high, as opposed to low, doses.

It is important to note that intravenous injections or infusions of sodium ascorbate can provide blood levels of at least 13,000 microM/L. This is greatly in excess of levels obtained with oral doses.

The implications of the short excretion half-life are profound. Most studies of high dose vitamin C have involved daily oral doses.[115] Relatively rarely, twice daily doses have been employed. Typically, studies have used a long dose interval, relative to the excretion half-life. The result is that for the duration of these studies, plasma levels have remained close to the baseline for the majority of the time. Basic pharmacology suggests that under such conditions, the studied doses will have minimal clinical effects. Thus, results from published clinical studies of high dose vitamin C against the common cold and other infectious diseases may greatly underestimate the potential efficacy of the treatment.

Pharmacokinetic results from the US National Institutes of Health indicate that, in health young adults, maximum sustained blood plasma levels require at least 18 grams per day, taken in divided doses, at short intervals.[116] There have been no controlled clinical trials of vitamin C at these dose levels. However, the literature contains numerous anecdotal reports, indicating that higher levels of vitamin C can be effective against infectious diseases.[104] Despite the heated controversy,

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[111] Levine M. Vitamin C pharmacokinetics: implications for oral and intravenous use, *Annals of Internal Medicine*, 2004; 140(7): 533-537.

[112] Levine M, Conry-Cantilena C, Wang Y, Welch RW, Phillip W, Washko PW, Dhariwal KR, Park JB, Lazarrev A, Graumlich JF, King J, Cantilena LR. Vitamin C pharmacokinetics in healthy volunteers: Evidence for a recommended dietary allowance, *Proceedings of the National Academy of Sciences of the USA*, 1996; 93: 3704–3709.

[113] Benke KK. Modelling Ascorbic Acid Level in Plasma and Its Dependence on Absorbed Dose, *Journal of the Australasian College of Nutritional & Environmental Medicine*, 1999; 18(1): 11-12.

[114] Hickey S, Roberts HJ, Cathcart RF. (2006) Dynamic flow: a new model for ascorbate. *Journal of Orthomolecular Medicine*, [in press].

[115] Hickey S, Roberts H. (2004) *Ascorbate: the science of vitamin C*, Lulu Press.

[116] Padayatty SJ, Sun H, Wang Y, Riordan HD, Hewitt SM, Katz A, Wesley RA, Levine M. Vitamin C pharmacokinetics: implications for oral and intravenous use, *Annals of Internal Medicine*, 2004; 140(7): 533-537.

the efficacy of high dose vitamin C in viral disease and influenza remains a valid scientific hypothesis.

4.2.4 Pharmacokinetics in illness

The pharmacokinetics of ascorbate in the sick has not been investigated quantitatively. However, it is established that oral absorption and utilization is markedly changed.[117] The maximum tolerated single oral dose in a healthy adult varies, but is typically 2-3 grams. Larger doses induce diarrhoea, which is the only established toxicity.[118] However, during illnesses, such as the common cold or influenza, the bowel tolerance level is dramatically increased.[119] The existence of this phenomenon is uncontroversial.

A common cold can increase the bowel tolerance to 30-100 grams per day, while influenza patients can tolerate over 200 grams per day, without reaching bowel tolerance. The available information suggests that increased utilization occurs and facilitates the intestinal transport.[81] It is clear that the data on oral ascorbate pharmacokinetics in healthy people does not apply to the sick.

4.2.5 Nutritional doses

The required magnitude of nutritional doses of vitamin C is a subject of some debate. The dietary reference intakes (DRI) are set at a low level, of the order of 100mg per day, depending on the country concerned.[118] The tolerable upper limit is set at approximately 2 grams, based on minimum bowel tolerance alone. However, the current values for the DRI for vitamin C have come under vigorous attack on the basis of poor scientific methods. Hickey and Roberts published "Ridiculous Dietary Allowance" in 2005, suggesting that the basis of the DRI for ascorbate was flawed.[120]

Pharmacokinetic data indicate higher minimum levels, in the region of 2-3 grams per day, taken in divided doses, can create a "dynamic flow" of ascorbate through the body. This level of intake is claimed to optimize health and prevent infectious diseases, such as influenza, by placing the body in a reducing state. Hickey and Roberts' book was submitted to the US Institute of Medicine and the National Institutes of Health for comment before publication. Several thousand free copies were downloaded in an open scientific review, also prior to publication. No objections have yet been reported.

4.2.6 Therapeutic doses

After Pauling popularized the use of vitamin C as a treatment for disease, confusion occurred over the size of a therapeutic dose. Pauling originally proposed doses at the gram level for treatment, a level that was somewhat misleading. Therapeutic doses that were reported as effective in acute viral disease, for

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[117] Hickey S, Roberts HJ, (2004) *Ascorbate: the science of vitamin C*, Lulu press.

[118] Standing Committee on Dietary reference Intakes. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids: A Report of the Panel on Dietary Antioxidants and Related Compounds, *Institute of Medicine, National Academy Press, USA*, 2000.

[119] Cathcart RF. Vitamin C titrating to bowel tolerance, anascorbemia and acute induced scurvy, *Medical Hypotheses*, 1981; 7: 1359-1376.

[120] Hickey S, Roberts HJ. (2005) *Ridiculous Dietary Allowance*, Lulu press.

example, were much larger and were taken repeatedly, at short intervals.[81] The evidence for such treatments arises largely from numerous uncontrolled studies, but the magnitude of the reported response is large and unprecedented.[104,117]

Pharmacological doses of ascorbate are considered to be those above 10 grams per day. Intravenous doses are reported to be far more effective than oral doses and this is consistent with the known pharmacokinetics. The minimum oral dose for treating influenza would be at least 5 grams per hour, following a large loading dose. The patient is advised to reduce the dose slightly, as bowel tolerance is approached. Such intakes have never been subject to randomized controlled clinical trials, but are supported by anecdotal evidence and clinical reports from independent doctors, over a period of more than half a century. It is clearly unscientific to discount these reports without conflicting evidence.[117]

4.2.7 Possible mechanisms of antiviral and immune response

The principal mechanisms of morbidity and mortality in avian influenza are believed to be over-production of pro-inflammatory cytokines, predominantly TNF-alpha. The result is a "cytokine storm," leading to bronchopneumonia and disseminated haemorrhage. Here, we briefly describe evidence that vitamin C has substantial benefits in preventing the inflammation and free radical damage associated with viral infections. For example, vitamin C can inhibit replication of HIV.[121] Ascorbate suppresses the expression of the HIV virus by a mechanism independent of the expression of NF-KappaB.[122] A large diminution in the stimulation of HIV production by cytokines is also reported, especially for pharmacological concentrations of the vitamin, which can produce a remarkable order of magnitude decrease.[123]

4.2.8 Respiratory Infections

The effects of vitamin C on the common cold have been covered extensively in the literature,[124,125,126,127,128,129,130,131,132,133,134,135,136] but these studies apply to

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[121] Harakeh S, Jariwalla RJ, Pauling L. Suppression of human immunodeficiency virus replication by ascorbate in chronically and acutely infected cells. *Proceedings of the National Academy of Sciences of the USA*, 1990; 87: 7245-7249.

[122] Harakeh S, Jariwalla RJ. NF-kappa B-independent suppression of HIV expression by ascorbic acid. *AIDS Research and Human Retroviruses*, 1997; 13(3): 235-239.

[123] Harakeh S, Jariwalla RJ. Ascorbate effect on cytokine stimulation of HIV production. *Nutrition*, 1995; 11(5 Supplements): 684-687.

[124] Douglas RM, Hemilä H. Vitamin C for preventing and treating the common cold. *Public Library of Science and Medicine*, 2005; 6: e168.

[125] Hemila H. Vitamin C and the common cold, *British Journal of Nutrition*, 1992; 67(1): 3-16.

[126] Hemila H. Does vitamin C alleviate the symptoms of the common cold? - a review of current evidence. *Scandinavian Journal of Infectious Diseases*, 1994; 26(1): 1-6.

[127] Hemila H. Vitamin C. The placebo effect, and the common cold: a case study of how preconceptions influence the analysis of results. *Journal of Clinical Epidemiology*, 1996; 49(10): 1079-1084.

relatively small, gram level, doses, taken at long intervals relative to the excretion half-life. Such studies are likely to underestimate the effectiveness of ascorbate. Notably, a single dose of 8 grams has been reported to be more effective as a treatment.[124] This higher dose may transiently approach the claimed minimum therapeutic range of the anecdotal studies. Despite the majority of studies having the methodological flaw described above, there have been several reports of benefits, even with far from optimal doses.

In acquired respiratory distress syndrome, the antioxidant status is compromised,[137] with depleted levels of vitamin C,[138] resulting in free radical damage and massive oxidative stress. Normal dietary intakes of vitamin C and other nutrients are insufficient to compensate for this failure,[139] but may have a positive effect.[138] However, from basic pharmacological principles, a sufficiently large dose of ascorbate would place the tissue in a more reducing state.[81] Schorah *et al.* found that plasma ascorbic acid levels in critically ill patients were 25% of

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[128] Hemila H. Vitamin C supplementation and common cold symptoms: problems with inaccurate reviews. *Nutrition*, 1996; 12(11-12): 804-809.

[129] Hemila H. Vitamin C supplementation and the common cold - was Linus Pauling right or wrong? *International Journal for Vitamin and Nutrition Research*, 1997; 67(5): 329-335.

[130] Gorton HC, Jarvis K. The effectiveness of vitamin C in preventing and relieving the symptoms of virus-induced respiratory infections. *Journal of Manipulative and Physiological Therapeutics*, 1999; 22(8): 530-533.

[131] Van Straten M, Josling P. Preventing the common cold with a vitamin C supplement: a double-blind, placebo-controlled survey. *Advances in Therapy*, 2002; 19(3): 151-159.

[132] Audera C, Patulny RV, Sander BH, Douglas RM. Mega-dose vitamin C in treatment of the common cold: a randomised controlled trial, *The Medical Journal of Australia*, 2001; 175: 359-362.

[133] Anderson TN, Suranyi B, Beaton GW. The effect on winter illness of large doses of vitamin C. *Canadian Medical Association Journal*, 1974; 11: 31-38.

[134] Karlowski TR, Chalmers TC, Frenkel LD, Kapikian AZ, Lewis TL, Lynch JM. Ascorbic acid for the common cold, a prophylactic and therapeutic trial. *The Journal of the American Medical Association*, 1975; 231: 1038-1042.

[135] Elwood PC, Hughes SJ, St Leger AS. A randomized controlled trial of the therapeutic effect of vitamin C in the common cold. *Practitioner*, 1977; 218: 133-137.

[136] Tyrrell DA, Craig JW, Meada TW, White T. A trial of ascorbic acid in the treatment of the common cold. *British Journal of Preventive and Social Medicine*, 1977; 31: 189-191.

[137] Richards GA. Nutrition and Oxidants in the Critically Ill Patient. *Clinical Pulmonary Medicine*, 2004; 11(3): 183-187.

[138] Lang JD, McArdle PJ, O'Reilly PJ, Matalon S. Oxidant-Antioxidant Balance in Acute Lung Injury. *Chest Journal*, 2002; 122: 314S-320S.

[139] Metnitz PGH, Bartens C, Fischer M, Fridrich P, Steltzer H, Druml W. Antioxidant status in patients with acute respiratory distress syndrome. *Intensive Care Medicine*, 1999; 25(2): 180-185.

those in healthy controls.[140] Hunt *et al.* found a "significant" effect on symptom levels in elderly patients, hospitalised with respiratory infections, with a dose of 200 mg daily.[141] Bernasconi and Massera gave 300 mg ascorbic acid (with 500 mg aspirin) twice daily to 39 influenza sufferers, and reported "rapid complete recovery" in all patients.[142] Gorton *et al.* reported an 85% decrease in influenza and cold symptoms after starting administration of 3000 mg upwards *per diem*.[143]

In 1942, Glazebrook & Thomson gave 50 to 100 mg of vitamin C to boarding school pupils, and observed complete prevention of pneumonia cases (no cases in 335 subjects in the vitamin C arm, against 17 in 1100 controls); there are a number of reasons not to regard this study as definitive.[144] Renker & Wegner, in 1954,[145] found that long-term supplementation of dock-workers with a (relatively low) daily 100 mg dose of ascorbic acid reduced rates of influenza infection by 28%.

Dahlberg *et al.* found a 50% reduction in more serious respiratory infections with 500 mg daily.[146] Pitt & Costrini administered 2000 mg daily to US marine recruits and, although there was no reduction in incidence of the common cold, there was an 85% reduction in more serious infections, including pneumonia.[147]

The literature on treatment of flu using pharmacological doses of vitamin C is limited. In 1963, Magne reported treating 130 cases with variable doses, up to 45 grams.[148] Of these subjects, 114 recovered well in three days, while 16 did not respond. Levy explains the lack of reaction in a small number of subjects as a biological response to the variable doses administered.[104] A recent Bulgarian study, in mice, sought to find the effect of injections of vitamins C and E on free

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[140] Schorah CJ, Downing C, Piripitsi A, Gallivan L, Al-Hazaa AH, Sanderson MJ, Bodenham A. Total vitamin C, ascorbic acid, and dehydroascorbic acid concentrations in plasma of critically ill patients. *American Journal of Clinical Nutrition*, 1996; 63: 760-765.

[141] Hunt C, Chakravorty NK, Annan G. The clinical and biochemical effects of vitamin C supplementation in short-stay hospitalized geriatric patients. *International Journal for Vitamin and Nutrition Research*, 1984; 1: 65-74.

[142] Bernasconi P, Massera E. Evaluation of a new pharmaceutical form of nimesulide for the treatment of influenza. *Drugs Under Experimental and Clinical Research,* 1985; 10: 739-743.

[143] Gorton HC, Jarvis K. The effectiveness of vitamin C in preventing and relieving the symptoms of virus-induced respiratory infections. *Journal of Manipulative and Physiological Therapeutics*, 1999; 8: 530-533.

[144] Glazebrook AJ, Thomson S. The administration of vitamin C in a large institution and its effect on general health and resistance to infection. *J Hygiene (London)*, 1942: 1-19.

[145] Renker K, Wegner S. Vitamin C prophylactics in the shipyard of Stralsund. *Das Deutsche Gesundheitswesen*, 1954: 22: 702-706.

[146] Dahlberg G, Engel A, Rydin H. The value of ascorbic acid as a prophylactic against common colds*. Acta Medica Scandinavica (Stockholm)*, 1944; 540-561.

[147] Pitt HA, Costrini AM. Vitamin C prophylaxis in marine recruits. *The Journal of the American Medical Association,* 1979; 9: 908-911.

[148] Magne RV. Vitamin C in treatment of influenza. *El Dia Medico*, 1963; 35: 1714-1715.

radical diseases, particularly influenza.[149] The study indicated that vitamin E reduced lipid peroxidation during the infection. Vitamin C showed a similar, smaller effect, but potentiated the action of vitamin E. This study suggested that vitamin C acted by chemically reducing the oxidized vitamin E, thus increasing its effects. The results imply that vitamin C could be even more effective if given frequently, as only a single dose was used and the half-life is short.[117]

The effects of frequent, pharmacological (large) doses of vitamin C have been reported to be highly effective in uncontrolled studies, over a time span of almost 60 years. However, the controlled trials have covered a lower dose range, given over inappropriately long intervals of time. The claims that high dose vitamin C can be used to treat and prevent infections are valid scientific hypotheses, with experimental, animal and surprisingly persuasive anecdotal support. The reason the controversy remains is that the appropriate clinical trials, using adequate dosing regimes, have not been performed.

4.2.9 Cost benefit analysis

A simple cost benefit analysis of the use of vitamin C in prevention of disease is useful. Vitamin C is cheap, easily available and has an outstanding safety record. The costs of using it as a preventative for avian flu are relatively low. Even if the detractors were correct and it was only marginally effective, it would still be of benefit as a preventative under pandemic conditions. If, as seems likely, repeated doses increase its effectiveness, then the preventative benefits could be outstanding.

The cost benefit analysis in therapy is powerful and persuasive. A person with avian flu may have a risk of death approaching 50%. If massive sustained doses of vitamin C are given to the patient, the risks associated with treatment are minimal. However, if the anecdotal reports are only partially correct, the benefits are substantial. There appears to be no viable scientific rationale for not trying pharmacological doses of ascorbate with avian flu victims.

4.2.10 Cytokine storm

There is evidence that ascorbate could ameliorate the effects of cytokine storm, which have been associated with avian flu. An oxidising environment leads to enhanced release of superoxide and nitric oxide, activation and translocation of NF-KappaB and enhanced production of cytokines. These cytokines include tumour necrosis factor-α, interleukin (IL)-1ß and IL-12. The creation of a markedly reducing environment, by addition of antioxidants, limits these primary immune responses in the lung.[150,151] A reduction of cytokines and their effects is also seen

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[149] Tantcheva LP, Stoeva ES, Galabov AS, Braykova AA, Savov VM, Mileva MM. Effect of vitamin E and vitamin C combination on experimental influenza virus infection. *Methods and Findings in Experimental and Clinical Pharmacology*, 2003; 25(4): 259-264.

[150] Crapo JD. Oxidative stress as an initiator of cytokine release and cell damage. *The European Respiratory Journal Supplement*, 2003; 44: 4s-6s.

[151] Payne JP, Moreno T, Richards RJ, Kelly FJ, Tetley TD. Particle-induced oxidative stress and cytokine release is attenuated by lung antioxidants in human alveolar macrophages and type 2 epithelial cells. *Experimental Lung Research*, 2003; 29(6): 421-444.

with ascorbate in other conditions and tissues, such as the heart.[152] Furthermore, vitamins C and E increase resistance of human dendritic cells to phenotypic and functional changes following stimulation with proinflammatory cytokines.[153]

Nieman *et al*. found that administration of 1500 mg ascorbate daily to marathon runners significantly reduced (range -26% to -57%) plasma cytokine levels after a race.[154] Hirai *et al*. found a combination of ascorbate and alpha-tocopherol to be superior to methylprednisolone in reducing post-thoracotomy cytokine storm.[155]

As is the case with most agents, there is currently no direct laboratory evidence of the effects of vitamin C in avian influenza. Human studies show a clinical effect that is clearly consistent with vitamin C producing a reduction in pro-inflammatory cytokines in viral infection of the lung. For example, in a study of critically ill surgical patients, pulmonary morbidity was lessened by antioxidant supplementation.[156] Consistent with this is the finding that the total antioxidant status correlates well with the severity of acquired pneumonia, providing an indication for vitamin C and other antioxidants in therapy.[157]

4.2.11 Prevention

Vitamin C has the advantage of being inexpensive and readily available, in large quantities. The minimum dose of vitamin C postulated to increase resistance to infection with influenza is 2-3 grams per day. This needs to be taken in divided doses, for example, 6 doses of 500 mg, taken at equal intervals throughout the day. This repeated dosing is important, because of the short elimination half-life. Sustained release formulation may help maintain plasma levels. In an epidemic, higher levels may provide increased protection. In a healthy adult, the upper limit of absorption for a single oral dose occurs with an intake of 2-3 grams. Intakes of 3 grams every 4 hours lead to plasma saturation in normal, healthy adults.

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[152] Horton JW, White DJ, Maass DL, Hybki DP, Haudek S, Giroir B. Antioxidant vitamin therapy alters burn trauma-mediated cardiac NF-kappaB activation and cardiomyocyte cytokine secretion. *The Journal of Trauma*, 2001; 50(3): 397-406, discussion 407-8.

[153] Tan PH, Sagoo P, Chan C, Yates JB, Campbell J, Beutelspacher SC, Foxwell BM, Lombardi G, George AJ. Inhibition of NF-kappa B and oxidative pathways in human dendritic cells by antioxidative vitamins generates regulatory T cells. *Journal of Immunology*, 2005; 174(12): 7633-7644.

[154] Nieman DC, Peters EM, Henson DA, Nevines EI, Thompson MM. Influence of Vitamin C Supplementation on Cytokine Changes Following an Ultramarathon. *Journal of Interferon & Cytokine Research*, 2000; 20(11): 1029-1035.

[155] Hirai T, Matsumoto H, Yamashita K, Urakami A, Iki K, Yamamura M, Tsunoda T. Surgical oncotaxis-excessive surgical stress and postoperative complications contribute to enhancing tumor metastasis, resulting in a poor prognosis for cancer patients. *Annals of Thoracic and Cardiovascular Surgery*, 2005; 1: 4-6.

[156] Nathens AB, Neff MJ, Jurkovich GJ, Klotz P, Farver K, Ruzinski JT, Radella F, Garcia I, Maier RV. Randomized, prospective trial of antioxidant supplementation in critically ill surgical patients. *Annals of Surgery*, 2002; 236(6); 814-822.

[157] Katsoulisa K, Kontakiotisa T, Baltopoulosc G, Kotsovilib A, Legakisb IN. Total Antioxidant Status and Severity of Community-Acquired Pneumonia: Are They Correlated? *Clinical Investigations*, 2005; 72: 335-344.

4.2.12 Treatment

Oral treatment with ascorbate needs to occur immediately the infection is suspected. Waiting for definitive symptoms to appear allows the infection to take hold; reports suggest it would then become far more difficult to treat. The minimum dose for treating avian flu would begin at a minimum of 8 grams, taken every 30 minutes, in the first instance. The dose could be reduced as bowel tolerance is approached. The treatment is claimed to be effective when the patient is kept continuously close to bowel tolerance.

Studies on the effectiveness of intravenous sodium ascorbate in avian influenza patients are urgently required. Intravenous treatment requires an infusion of sodium ascorbate, as ascorbic acid can damage the vasculature at the injection site. Such treatment is combined with oral doses. This treatment is reported to be far more effective than oral doses, which is consistent with the known pharmacokinetics.

4.3 VITAMIN B12

Consideration of vitamin B12 in this report relates exclusively to its potential usefulness in the event of a HPAI pandemic, specifically in relation to treatment of cytokine storm.

In inflammation, including acute infection, there are marked increases in levels of transcobalamins and general B12 binding capacity, and cobalamins.[158] In cobalamin deficiency there is a linear inverse relationship between cobalamin and TNF-alpha levels.[159] In 1951, Howard & deBakey showed that B12 was effective in the treatment of haemorrhagic shock.[160] Units in France, Spain, Italy and in Asia have used very high doses of cobalamins for the treatment of cyanide poisoning for several decades, with remarkable success within 48 hours in many cases,[161,162,163] and equally remarkable safety.[164] In vitro evidence shows that cobalamins cause a partial suppression of inflammatory cytokines IL-6 and NFkappa-B.[165] Partial suppression is necessary and important, as studies on synthetic anti-cytokine agents such as anti-TNF-alpha antibodies show that they can suppress immunity too effectively, leading to vulnerability to secondary infections.[166] Cobalamin has the further useful property of nitric oxide and peroxynitrite quenching.[167] thus inhibiting both tissue damage and cytokine activation by this major reactive oxygen species.

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[158] Nexo E. (1998) Cobalamin Binding Proteins. Eds. Kräutler B, Arigoni D, Golding BT. *Vitamin B12 and B12 Proteins*. Wiley: La Jolla. 57-85.

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[160]Howard JM, de Bakey ME. The treatment of hemorrhagic shock with cortisone and vitamin B12. *Surgery*, 1951; 30: 161-65.

[161] Yacoub M, Faure J, Morena M, Vincent M, Faure H. (In French.) L`intoxication cyanhydrique aiguë. Données actuelles sur le métabolisme du cyanure et le traitement par hydroxocobalamine. *Journal European de Toxicology*, 1974; 7: 22-29.

[162] Motin J, Bouletrean P, Rouzious JM. (In French.) Intoxication cyanhydrique grave traitée avec succès par hydroxocobalamine. *Journal de Medecine Legale Droit Medical*, 1970; I: 717-22.

[163] Hall AH, Rumack BH, Hydroxocobalamin/sodium thiosulfase as a cyanide antidote. *Journal of Emergency Medicine*, 1987; 5: 115-21.

[164] Forsyth JC, Mueller PD, Becker CE, et al. Hydroxocobalamin as a cyanide antidote: safety, efficacy and pharmacokinetics in heavily smoking normal volunteers. *Clinical Toxicology*, 1993; 31**:** 277-94.

[165] Yamashiki M, Nishimura A, Kosaka Y. Effects of methylcobalamin (vitamin B12) on in vitro cytokine production of peripheral blood mononuclear cells. *Journal of Clinical and Laboratory Immunology*, 1992; 37: 173-82.

[166] Reinhart K, Karzai W. Anti-tumor necrosis factor therapy in sepsis: update on clinical trials and lessons learned. *Critical Care Medicine*, 2001; 29: S121-S125.

[167] Kruszyna H, Magyar JS, Rochelle LG, et al. Spectroscopic studies of nitric oxide (NO) interactions with cobalamins: reaction of NO with superoxocobalamin (III) likely accounts

All the available evidence therefore points to cobalamin being a useful and safe inhibitor of cytokine storm, of which there is no demonstrated pharmaceutical agent of proven efficacy. While there is no conclusive study to show that cobalamin will save lives in this situation, there is equally no pharmaceutical agent which has been shown to work consistently, and much evidence that such agents are often both ineffective and unsafe.[168]

for cobalamin reversal of the biological effects of NO. *Journal of Pharmacology and Experimental Therapeutics*, 1998; 285: 665-71.

[168] Riedemann NC, Guo R-F, Ward PA. Novel Strategies for the treatment of sepsis. *Nature Medicine*, 2003; 9 (5)**:** 517-524.

4.4 VITAMIN A (AND RETINOIDS)

Vitamin A is known to be essential for normal growth,[169] for cell maturation, particularly neurodevelopment; for cell membrane stability, for visual[170] and skin health[171], and as an antioxidant, as well as for immunity. Moreover it is required not only for the normal functioning of both the cell-mediated and humoral arms of acquired immunity, but even more so for innate immunity.[172]

Vitamin A deficiency is recognised as one of the 'big three' micronutrient deficiencies worldwide (the others being iron and iodine), and it is recognised that this can severely impair immunity, and lead to increases in morbidity and mortality in affected populations, particularly in children.[173] That this is not only an issue for developing countries is shown by the surprising finding that 50% of children with measles in Long Beach, California assessed in a 1992 study were vitamin A deficient.[174] It is further recognised that in populations with already marginal vitamin A status, infectious diseases can precipitate overt deficiency of vitamin A, thereby further exacerbating the morbidity.[175]

Much evidence exists that humoral immunity (antibody-mediated immunity, Th-2) is impaired in vitamin A deficiency,[176] [177] the potential consequences of this in the context of avian flu are principally increased susceptibility to, and morbidity from,

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[169] Bahl R, Bhandari N, Taneja S, Bhan MK. The impact of vitamin A supplementation on physical growth of children is dependent on season. *European Journal of Clinical Nutrition*. 1997; 51(1):26-29.

[170] Cohen N, Rahman H, Mitra M, Sprague J, Islam S, Leemhuis de Regt E, Jalil MA. Impact of massive doses of vitamin A on nutritional blindness in Bangladesh. *American Journnal of Clinical Nutrition*. 1987; 45(5): 970-976.

[171] Saurat JH. Skin, sun, and vitamin A: from aging to cancer. *Journal of Dermatology*. 2001; 28(11): 595-598.

[172] Stephensen CB. Vitamin A, infection, and immune function. *Annual Review of Nutrition*. 2001; Vol.21: 167-192.

[173] Fawzi WW, Herrera MG, Willett WC, Nestel P, el Amin A, Mohamed KA. Dietary vitamin A intake and the incidence of diarrhea and respiratory infection among Sudanese children. *The Journal of Nutrition*. 1995; 125(5): 1211-1221.

[174] Arrieta AC, Zaleska M, Stutman HR, Marks MI. Vitamin A levels in children with measles in Long Beach, California. *The Journal of Pediatrics*. 1992; 121(1): 75-78.

[175] Semba RD. Vitamin A and immunity to viral, bacterial and protozoan infections. *The Proceedings of the Nutrition Society*. 1999; 3: 719-727.

[176] Cantorna MT, Nashold FE, Hayes CE. In vitamin A deficiency multiple mechanisms establish a regulatory T helper cell imbalance with excess Th1 and insufficient Th2 function. *The Journal of Immunology*. 1994; 4: 1515-1522.

[177] Jason J, Archibald LK, Nwanyanwu OC, Sowell AL, Buchanan I, Larned J, Bell M, Kazembe PN, Dobbie H, Jarvis WR. Vitamin A levels and immunity in humans. *Clinical and Diagnostic Laboratory Immunology*. 2002; 3: 616-621.

secondary (largely bacterial) infections.[178] Vitamin A supplementation either in anticipation of, or at the onset of infection can greatly reduce morbidity.[179]

However cellular immunity (cell-mediated, Th-1) is also dependent on vitamin A status; deficiency causes impairment well before any other symptoms or signs,[180] and supplementation can normalise cellular immunity within about 3 days.[181,182] It is this aspect of immune functioning that is necessary for handling viruses, as well as yeasts and intracellular bacteria. A number of studies have shown that vitamin A status correlates inversely with severity of viral infections, particularly measles,[183,184] and this is the case even in the supposedly well-nourished USA.[185]

An equally important role of vitamin A, however, is in supporting innate immunity in the gut and other mucosal surfaces (also known as Th-3). Mucosal integrity and levels of secretory IgA are reduced in vitamin A deficiency,[186] and increase with vitamin A levels,[187] This represents the primary barrier against viral infection.

Vitamin A is therefore necessary for all aspects of immune defence, and improvement of vitamin A status can improve all these aspects. Some studies have found that very high doses can impair Th-1 function,[188] but these amount to a broad dose-finding exercise, indicating that the dose levels we propose herein (see Protocols in Section 7.2.2 of report) will augment all aspects of immune

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[178] Sherwani MK, Chaudhry NA, Hashmi AS, Anjum AD. Studies on the effect of vitamin A deficiency on humoral immunity. *Journal of the Pakistan Medical Association*. 1980; 10: 224-227.

[179] Semba RD. Vitamin A, immunity, and infection. *Clinical Infectious Diseases (Infectious Diseases Society of America)*. 1994; 19(3): 489-499.

[180] Smith SM, Levy NS, Hayes CE. Impaired immunity in vitamin A-deficient mice. *The Journal of Nutrition*. 1987; 5: 857-865.

[181] Athanassiades TJ. Adjuvant effect of vitamin A palmitate and analogs on cell-mediated immunity. *Journal of the National Cancer Institute*. 1981; 5: 1153-1156.

[182] Nuwayri-Salti N, Murad T. Immunologic and anti-immunosuppressive effects of vitamin A. *Pharmacology*. 1985; 4: 181-187.

[183] D'Souza RM, D'Souza R. Vitamin A for preventing secondary infections in children with measles--a systematic review. *Journal of Tropical Pediatrics*. 2002; 2: 72-77.

[184] D'Souza RM, D'Souza R. Vitamin A for treating measles in children. *Cochrane Database Systematic Reviews.* 2002; 1: CD001479.

[185] Butler JC, Havens PL, Sowell AL, Huff DL, Peterson DE, Day SE, Chusid MJ, Bennin RA, Circo R, Davis JP. Measles severity and serum retinol (vitamin A) concentration among children in the United States. *Pediatrics.* 1993; 6: 1176-1181.

[186] Chandra RK, Wadhwa M. Nutritional modulation of intestinal mucosal immunity. *Immunological Investigations*. 1989; 1-4: 119-126.

[187] Thurnham DI, Northrop-Clewes CA, McCullough FS, Das BS, Lunn PG. Innate immunity, gut integrity, and vitamin A in Gambian and Indian infants. *The Journal of Infectious Diseases*. 2000; 182 Supp 1: S23-8.

[188] Cui D, Moldoveanu Z, Stephensen CB. High-level dietary vitamin A enhances T-helper type 2 cytokine production and secretory immunoglobulin A response to influenza A virus infection in BALB/c mice. *The Journal of Nutrition.* 2000; 5: 1132-1139.

function, while doses an order of magnitude higher will probably impair Th-1 functioning.

4.5 SILVER

Silver is not generally regarded as a nutrient, and so is an exception to the group of micronutrients considered in this section of the report. Many silver salts are actually of relatively high toxicity to humans and other mammals.[189,190]

However, there is an increasing body of evidence to suggest that low concentrations of ionic or oligodynamic silver have potent anti-viral effects, while demonstrating a very favourable toxicity profile at around 10 ppm / 2 ml dosages.

Feng *et al.* (2000)[191] showed that pathogen cell membranes, cytosol proteins and enzymes, nuclear membranes and genetic materials are all subject to the bactericidal effects of silver ions. Oka *et al.* (1994)[192] demonstrated that viral envelopes were inactivated by silver ions, while Zhang *et al.* (1991)[193] has shown that silver ions are first rate inhibitors of HIV's rennin and protease content.

In the case of H5N1, the following targets may be prime candidates for the viricidal action of silver ions (e.g., cleavage, inactivation and denaturing actions): viral envelope, hemagglutinin, neuraminidase; matrix proteins M1 and M2; nucleocapsid, nucleoproteins, 8 genes of H5N1, RNA, and RNA polymerases.

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[189] Grier N. 1983. Silver and its Compounds. In: *Disinfection, Sterilization and Preservation*. (Ed. Block S), Lea & Febiger: Philadelphia, PA, p. 380.

[190] Horner HC, Roebuck BD, Smith RP, English JP. Acute toxicity of some silver salts of sulfonamides in mice and the efficacy of penicillamine in silver. *Drug Chemistry and Toxicology*, 1983; 6(3): 267-77.

[191] Feng QL, Wu J, Chen GQ, Cui FZ, Kim TN, Kim JO, A Mechanistic Study of the Antibacterial effect of Ag+ Ions on Escherichia coli and Staphylococcus aureus, *Journal of Biomedical Materials Research*, 2000; 52(4): 662-668.

[192] Oka M, Tomioka T, Tomita K, Nishino A, Ueda S. Inactivation of Enveloped Viruses by a Ag+-Thiosulfate Complex. *Metal-Based Drugs*, 1994; 1(5-6): 511.

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4.6 OTHER MICRONUTRIENTS

Other micronutrients are known to be of importance in supporting the immune system, including the vitamins E,[194] B6[195] and various carotenoids,[196] as well as the minerals selenium,[197] iron,[198] copper[199] and manganese.[200] Other nutrient groups such as Omega-3 essential fatty acids derived from fish oils are also beneficial for cytokine modulation in the immune system.[201]

In the event of pandemic, where normal dietary regimes are compromised owing to food supply problems, deficiencies of these nutrients are considerably more likely than in non-pandemic situations.

Adverse effects from low intakes can be countered by careful attention to diet and/or supplementation programmes. Good quality multivitamin and mineral complexes and fish oil supplements may provide important additional intakes of such micronutrients.[202,203]

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[194] Beharka A, Redican S, Leka L, Meydani SN. Vitamin E status and immune function. *Methods in Enzymology*, 1997; 282: 247-63. Review.

[195] Chandra RK. Nutrition and immunology: from the clinic to cellular biology and back again. *Proceedings of the Nutrition Society*, 1999; 58(3): 681-3. Review.

[196] Chew BP, Park JS. Carotenoid action on the immune response. *Journal of Nutrition*, 2004; 134(1): 257S-261S. Review.

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[198] Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. *Journal of Nutrition*, 2001; 131(2S-2): 568S-579S; discussion 580S. Review.

[199] Bonham M, O'Connor JM, Hannigan BM, Strain JJ.The immune system as a physiological indicator of marginal copper status? *British Journal of Nutrition*, 2002; 87(5): 393-403. Review.

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[202] Wood SM, Beckham C, Yosioka A, Darban H, Watson RR. beta-Carotene and selenium supplementation enhances immune response in aged humans. *Integrative Medicine*, 2000; 2(2): 85-92.

[203] Bjornsson S, Hardardottir I, Gunnarsson E, Haraldsson A.Scand J Infect Dis. Dietary fish oil supplementation increases survival in mice following Klebsiella pneumoniae infection. 1997; *Scandinavian Journal of Infectious Diseases*, 29(5): 491-3.

5. BOTANICAL AND MICRO-ORGANISM DERIVED SUBSTANCES

There are a wide range of botanical or micro-organism-derived products which may be able to play a valuable role in supporting the body or immune system during an HPAI pandemic. Dealing with each is beyond the scope of this report, particularly given intrinsic variability between botanical products as a result of different extraction methods, growing conditions, selection of plant parts and standardization procedures.

However, a number of botanicals have been considered briefly, and some evidence for their possible usefulness in relation to immune enhancement or modulation effects following a cytokine over-response or cascade, as is typical following human infection by HPAI H5N1 virus, has been provided.

The ANH is linked to a number of herbal associations and companies that have specific expertise and products that could potentially be of value in mitigating the cytokine storm and supporting the immune system during an H5N1 pandemic. Should further research be required, this expertise could be brought to bear in the development and implementation of specific studies and trials.

5.1 BETA GLUCANS

Of the natural compounds known to stimulate the humoral (innate or non-specific) immune system, one of the best documented and most effective are the 1-3, 1-6 beta glucans, generally derived from brewer's yeast[204,205] or found within mushrooms such as shiitake (containing lentinan) and maitake.[206] Mushroom glucans are always heterogeneous, but lentinan has such a large molecular weight (400,000 – 1,000,000 daltons) that it is reported to be poorly bioavailable orally, thus requiring intravenous injection.[207] Lentinan, administered both intranasally and intravenously, prior to challenge with influenza A virus, significantly increased non-specific immune responses as determined by assessing respiratory burst of broncho-alveolar macrophages.[208]

'Immunoceuticals' have actually been recorded from some 50 species of mushroom, many of these being beta glucans with demonstrated anti-cancer and immune modulation activity.[207]

These molecules activate the innate immune system in humans and other animals[209,210] Macrophages have receptors that specifically recognise 1-3, 1-6 beta glucans[211] because they occur in the cell walls of many bacteria and fungi. Consumption of beta glucans is thought to stimulate production of various aspects

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[204] Kernodle DS, Gates H, Kaiser AB. Prophylactic anti-infective activity of poly-(1-6)-beta-D-glucapyranosyl-(1-3)-beta-D-glucapyranose glucan in a guinea pig model of staphylococcal wound infection. *Antimicrobial Agents & Chemotherapy,* 1998; 42: 545-9.

[205] Wakshull E, Brunke-Reese D, Lindermuth J, Fisette L, Nathans RS, Crowley JJ, Tufts JC, Zimmerman J, Mackin W, Adams DS. PGG-glucan, a soluble beta-(1,3)-glucan, enhances the oxidative burst response, microbicidal activity, and activates an NF-kappa B-like factor in human PMN: evidence for a glycosphingolipid beta-(1,3)-glucan receptor. *Immunopharmacology*. 1999; 41(2): 89-107.

[206] Wasser SP, Weis AL. Therapeutic effects of substances occurring in higher basidiomycetes mushrooms: a modern perspective. *Critical Reviews in Immunology*, 1999; 19: 65-96.

[207] Kidd PM. The use of mushroom glucans and proteoglycans in cancer treatment. *Alternative Medicine Review*, 2000; 5(1): 4-27.

[208] Irinoda K, Masihi KN, Chihara G, Kaneko Y, Katori T. Stimulation of microbicidal host defence mechanisms against aerosol influenza virus infection by lentinan. *International Journal of Immunopharmacology*, 1992; 14(6): 971-7.

[209] Mansell PWA, Ichinose I-I, Reed RJ, Krements ET, McNamee RB, Di Luzio NR: Macrophage-mediated destruction of human malignant cells in vivo. *Journal of the National Cancer Institute,* 1975; 54: 571-80.

[210] Hahn MG, Albersheim P. Host-pathogen interactions. XIV. Isolation and partial characterization of an elicitor from yeast extract. *Plant Physiology,* 1978; 62: 107.

[211] Czop JK, Austen KF. A b-glucan inhibitable receptor on human monocytes: its identity with the phagocytic receptor for particulate activators of the alternative complement pathway. *Journal of Immunology,* 1985; 134: 2588-93.

of the humoral immune system and several well-conducted research papers have shown that resistance to infection may be enhanced greatly [212,213]

The beta glucans' ability to activate macrophages has been extensively tested[214,215,216,217,218] and has been shown to protect animals such as mice against otherwise fatal infections.[219,220] Trials have shown the same substantial protective effects in human infections.[221,222,223]

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[212] Onderdonk AB, Cisneros RL, Hinkson P, Ostroff G. Anti-infective effect of poly-beta-1,6-glucotriosyl-beta 1,3glucapyranose glucan *in vivo*. *Infection & Immunity* 1992; 60: 1642-7.

[213] Vetvicka V, Terayama K, Mandeville R, Brousseau P, Kournikakis B, Ostroff G. Pilot study: Orally-administered east beta1,3-glucan prophylactically protects against anthrax infection and cancer in mice. *Journal of the American Nutraceutical Association*, 2002; 5: 1-5.

[214] Rasmussen LT, Fandrem Jr. and Seljelid R. Dynamics of blood components and peritoneal fluid during treatment of murine *E. coli* sepsis with beta-1, 3-D-polyglucose derivatives. *Scandinavian Journal of Immunology,* 1985; 63: 73-80.

[215] Rasmussen LT, Seljelid R. Production of prostaglandin E2 and interleukin 1 by mouse peritoneal macrophages stimulated with beta-1, 3-D-glucan derivatized plastic beads. *Scandinavian Journal of Immunology*, 1987; 26(6): 731-6.

[216] Rasmussen LT, Seljelid R. The modulatory effect of lipoproteins on the release of interleukin 1 by human peritoneal macrophages stimulated with beta 1 -3D-polyglucose derivatives. *Scandinavian Journal of Immunology,* 1989; 29: 477-84.

[217] Rasmussen LT, Seljelid R, Dynamics of blood components and peritoneal fluid during treatment of murine *E. coli* sepsis with beta-1, 3-D-polyglucose derivatives. II. Interleukin 1, tumour necrosis factor, prostaglandin E2 and leukotriene B4. *Scandinavian Journal of Immunology* 1990; 32(4): 333-40.

[218] Rasmussen LT and Seljelid, R. Novel immunomodulators with pronounced *in vitro* effects caused by stimulation of cytokine release, *Journal of Cell Biochemistry,* 1991;46: 60-8.

[219] Williams DL, Diluzio NR. Glucan-induced modification of murine viral hepatitis. *Science,* 1980; 208: 67-9.

[220] Williams DL, Diluzio NR**.** Glucan induced modification of experimental Staphylococcus aureus infection in normal, leukemic and immunosuppressed mice. *Advances in Experimental Medical Biology*, 1979; 121(A): 291-306.

[221] de Felippe JJ, da Rocha-Silva FM, Maciel FM, Soares A de M, Mendes NF. Infection prevention in patients with severe multiple trauma with the immunomodulator beta 1-3 polyglucose (glucan). *Surgery, Gynecology and Obstetrics,* 1993; 177(4): 383-8.

[222] Babineau TJ, Hackford A, Kenler A, Bistrian B, Forse RA, Fairchild PG, Heard S, Keroack M, Caushaj P, Benotti P. A phase II multicenter, double-blind, randomized, placebo-controlled study of three dosages of an immunomodulator (PGG-glucan) in high-risk surgical patients. *Archives of Surgery*, 1994; 129(11): 1204-10.

The role of natural products such as beta glucans in supporting the humoral immune system, in combination with those which support the adaptive or cell-mediated immune system (such as zinc) should be explored as a matter of urgency in relation to H5N1 and other life threatening viral infections.

[223] Babineau TJ, Marcello P, Swails W, Kenler A, Bistrian B, Forse RA. Randomized phase I/II trial of a macrophage-specific immunomodulator (PGG-glucan) in high-risk surgical patients. *Annals of Surg*ery, 1994; 220(5): 601-9.

5.2 RESVERATROL

Resveratrol is a phytoalexin polyphenolic (stilbene) compound found in various plants, including grapes, berries, and peanuts. There is compelling evidence demonstrating beneficial effects on neurological, hepatic, and cardiovascular systems. Resveratrol has become particularly well recognised in recent years for its powerful role as a cancer chemo-preventative agent, but central to its putative mechanism of action, is its role in immune system modulation.

In a 2005 review, de la Lastra & Villegas present research demonstrating possible mechanisms for resveratrol's biological activities including the down-regulation of the inflammatory response through inhibition of synthesis and release of pro-inflammatory mediators, modification of eicosanoid synthesis, inhibition of activated immune cells, or inhibition of enzymes such as inducible nitric oxide synthase (NOS) and cyclooxygenase-2 (COX-2) via its inhibitory effects on nuclear factor-kappa B or the activator protein-1 (AP-1).[224]

An *in vitro* study by Wirleitner *et al.* (2005) showed suppression of specific Th-1 cytokines such as IFN-gamma. It would be valuable to demonstrate, for example in a murine model with an H5N1 challenge, whether this effect limited morbidity by limiting cytokine cascades.[225] In an *in vivo* study, cytokine (IL-2, NF-kappaB) suppression was noted following allograft rejection in rats.[226]

Given that one of the most important cytokines that is over-stimulated by H5N1 infection is TNF-alpha, which has the potential to trigger cytokine storm, it is of note that Gao *et al.* (2001) [227] determined that resveratrol suppresses TNF-alpha as well as IL-2. However, these authors also found this suppression to be "irreversible", which clearly could be of concern and requires further evaluation.

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[224] de la Lastra CA, Villegas I. Resveratrol as an anti-inflammatory and anti-aging agent: Mechanisms and clinical implications. *Molecular Nutrition & Food Research*, 2005; 49 (5): 405-430. Review.

[225] Wirleitner B, Schroecksnadel K, Winkler C, Schennach HS, Fuchs D. Resveratrol suppresses interferon-gamma-induced biochemical pathways in human peripheral blood mononuclear cells in vitro. *Immunology Letters*, 2005; 100 (2): 159-163.

[226] Wu SL, Pan CE, Yu L, Meng KW. Immunosuppression by combined use of cyclosporine and resveratrol in a rat liver transplantation model. *Transplantation Proceedings*, 2005; 37 (5): 2354-2359.

[227] Gao X, Xu YX, Janakiraman N, Chapman RA, Gautam SC. Immunomodulatory activity of resveratrol: suppression of lymphocyte proliferation, development of cell-mediated cytotoxicity, and cytokine production. *Biochemical Pharmacology*, 2001; 62(9): 1299-308.

5.3 GARLIC

Garlic (*Allium sativum* L.) has long been known to have medicinal properties, although these appear to be destroyed when garlic is cooked for culinary purposes.[228] There are a large number of garlic derivatives including allicin, which gives garlic, its characteristic taste and odour, and these have been shown to have benefits in the management of conditions such as lipidaemia and hypertension and anti-platelet effects.[229]

However, there is evidence that garlic has potent immuno-modulatory effects, which have been demonstrated in *in vitro* tests with peripheral blood cells,[230] as well as in animal models.[231]

Garlic extracts have also shown to have anti-viral properties.[228,232]

Hodge et al. (2002)[233] showed that T-cell IFN-gamma, IL-2, and TNF-alpha decreased significantly in the presence of ≤ 10 mcg / ml garlic extract while Chang et al (2005)[234] demonstrated differences in cytokine modulation between different garlic derivatives in activated macrophages. Diallyl sulphide suppressed all stimulated cytokines, and this inhibition appeared to be directly related to the suppression of nitric oxide (NO) and prostaglandin E_2 (PGE_2) production.

This and other work suggests that garlic derivatives may be of considerable value in supporting the immune system during a HPAI pandemic, but further work specific to H5N1 is required.

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[228] Harris JC, Cottrell SL, Plummer S, Lloyd D. Antimicrobial properties of *Allium sativum* (garlic). *Applied Microbiology & Biotechnology*, 2001; 57(3): 282-6. Review.

[229] Barnes J, Anderson LA, Phillipson JD. *Herbal Medicines*, 2002. Second edition. London: Pharmaceutical Press.

[230] Salman H, Bergman M, Bessler H, Punsky I, Djaldetti M. Effect of a garlic derivative (alliin) on peripheral blood cell immune responses. International Journal of *Immunopharmacology*, 1999; 21(9): 589-97.

[231] Ghazanfari T, Hassan ZM, Ebtekar M, Ahmadiani A, Naderi G, Azar A. Garlic induces a shift in cytokine pattern in *Leishmania* major-infected BALB/c mice. *Scandinavian Journal of Immunology*, 2000; 52(5): 491-5.

[232] Guo NL, Lu DP, Woods GL, Reed E, Zhou GZ, Zhang LB, Waldman RH. Demonstration of the anti-viral activity of garlic extract against human cytomegalovirus in vitro. *Chinese Medicine Journal (Engl)*, 1993; 106(2): 93-6.

[233] Hodge G, Hodge S, Han P. *Allium sativum* (garlic) suppresses leukocyte inflammatory cytokine production in vitro: potential therapeutic use in the treatment of inflammatory bowel disease. *Cytometry*, 2002; 48(4): 209-15.

[234] Chang HP, Huang SY, Chen YH. Modulation of cytokine secretion by garlic oil derivatives is associated with suppressed nitric oxide production in stimulated macrophages. *Journal of Agricultural Food Chemistry*, 2005; 53(7): 2530-4.

5.4 BLACK ELDERBERRY

Black elderberry (*Sambucus nigra* L.) extracts have been shown to protect against infection by certain viruses, probably both through direct viricidal activity as well as through stimulation of cytokines in the immune system. A proprietary product based on black elderberry has been shown to be beneficial in managing common forms of both influenza A and B infection.[235]

Elderberries contain a range of anthocyanidins which are know to be potent antioxidants. Common proprietary formulations are based on a 38% standardised elderberry extract.[236]

Although the anti-viral properties of *Sambucus* spp. have been widely reported, there is little or no published research elucidates its mechanism of action. Dr Madeleine Mumcuoglu, an Israeli virologist, has communicated that this action is caused by elderberry constituents which neutralize the activity of the haemagglutinin (H) spikes are found on the surface many viruses, including H5N1.[234] These H spikes are necessary for viral entry to cells and subsequent replication. However, this purported mechanism appears to be unpublished.

Further work by Barak *et al.* (2001), in a placebo-controlled, double-blind trial, demonstrated that black elderberry extracts function by stimulating cytokines such TNF-alpha and IL-1, IL-6 and IL-8.[237] In this study, induction of TNF-alpha was found to be 45-fold greater than in the controls. However, another study showed much lower cytokine induction (1.3-6.2-fold).[238]

Such stimulation needs to be well understood as it may present a risk in relation to triggering cytokine storm given the hyper-induction of cytokines known to occur following infection by HPAI H5N1. It may also suggest that the dosage specification is highly critical, perhaps complicating dose recommendations. Therefore, further research is required to determine both safety and efficacy of black elderberry extracts in relation to H5N1 infection.

Note: the authors of this report are aware of media reports suggesting that *in vitro* studies in the UK have demonstrated antiviral effects of a proprietary black elderberry extract against H5N1. Further studies are apparently also underway in Israel.

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[235] Zakay-Rones Z, Varsano N, Zlotnik M, Manor O, Regev L, Schlesinger M, Mumcuoglu M. Inhibition of several strains of influenza virus in vitro and reduction of symptoms by an elderberry extract (*Sambucus nigra* L.) during an outbreak of influenza B Panama. *Journal of Alternative & Complementary Medicine*, 1995; 1(4): 361-9.

[236] [No authors listed] Monograph. *Sambucus nigra* (elderberry). *Alternative Medicine Review*, 2005; 10(1): 51-4.

[237] Barak V, Halperin T, Kalickman I. The effect of Sambucol, a black elderberry-based, natural product, on the production of human cytokines: I. Inflammatory cytokines. *European Cytokine Network*, 2001; 12(2): 290-6.

[238] Barak V, Birkenfeld S, Halperin T, Kalickman I.The effect of herbal remedies on the production of human inflammatory and anti-inflammatory cytokines. *Israel Medical Association Journal*, 2002; 4(11 Suppl): 919-22.

5.5 ECHINACEA

Echinacea preparations from *Echinacea purpurea* and *E. angustifolia* are one of the most widely used herbal products for the common cold, in both Europe and the USA. Studies have shown considerable differences in activity between different preparations; Rininger *et al.* (2000) found that dried leaf and root powders acted as potent immuno-stimulants in murine and *in vitro* tests, while fresh juice extracts or extracts standardised to phenolic acid or echinacoside content were relatively inactive.[239]

A clinical study with a commercially available liquid tincture demonstrated clear efficacy of the product in reducing the severity and duration of symptoms of the common cold.[240] However, it appears from a review of 13 randomised, double blind, placebo controlled trials that Echinacea may be more effective in treating the early symptoms of common cold, than in its prevention.[241]

Gertsch et al. (2004)[242] identified a putative mechanism for the immuno-modulatory effects of certain Echinacea extracts, relating this to specific alkylamides (= alkamides), or cannabinoids, which modulate TNF-alpha mRNA expression in human monocytes/macrophages via the CB_2 cannabinoid receptor.

In a recent mechanistic, *in vitro* study using human whole blood, Raduner *et al.* (2006) demonstrated complex cytokine modulation affects triggered by specific alkylamides from Echinacea which caused up-regulation of IL-6 cytokine expression in an apparently CB_2-dependent manner, while causing down-regulation of TNF-alpha, IL-1 and IL-12 expression in a CB_2-independent manner.[243]

Such complexities of response for a given tincture, as well as differences in chemical composition between different products, make it difficult to draw any consistent and general conclusions over the potential for the use of Echinacea in a HPAI pandemic. It would be imperative to undertake *in vitro* and then *in vivo* studies with specific standardised extracts or products so that specific immune

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[239] Rininger JA, Kickner S, Chigurupati P, McLean A, Franck Z. Immunopharmacological activity of Echinacea preparations following simulated digestion on murine macrophages and human peripheral blood mononuclear cells. *Journal of Leukocyte Biology*, 2000; 68(4): 503-10.

[240] Brinkeborn RM, Shah DV, Degenring FH. Echinaforce and other Echinacea fresh plant preparations in the treatment of the common cold. A randomized, placebo controlled, double-blind clinical trial. *Phytomedicine*, 1999; 6(1): 1-6.

[241] Barrett B, Vohmann M, Calabrese C. Echinacea for upper respiratory infection. *Journal of Family Practice*, 1999; 48: 628-635. Review.

[242] Gertsch J, Schoop R, Kuenzle U, Suter A. Echinacea alkylamides modulate TNF-alpha gene expression via cannabinoid receptor CB2 and multiple signal transduction pathways. *FEBS Letters,* 2004; 577(3): 563-9.

[243] Raduner S, Majewska A, Chen JZ, Xie XQ, Hamon J, Faller B, Altmann KH, Gertsch J. Alkylamides from Echinacea are a new class of cannabinomimetics - CB2-receptor dependent and independent immunomodulatory effects. *Journal of Biological Chemistry*, 2006; [Epub ahead of print] (*http://www.jbc.org/cgi/reprint/M601074200v1*).

modulation responses to strains of the H5N1 virus can be evaluated. Based on the existing evidence, as is the case with some other botanical products, there is a risk that some Echinacea products might trigger cytokine storm if consumed at higher dosages.

5.6 OTHER NATURAL PRODUCTS

There are numerous other botanicals, micro-organism and animal derived products which have been shown to exhibit immune modulating activity of some type, but detailed consideration of these is beyond the scope of this report.

Natural products of interest include:

- Curcumin (*Curcuma longa*)[244]
- Cat's claw (*Uncaria guianensis or U. tomentosa*)[245]
- Astragalus (*Astragalus membranaceus*)[246]
- Sutherlandia (*Sutherlandia frutescens*)[247]
- Bovine thymus extracts[248]

[244] Terry CM, Clikeman JA, Hoidal JR, Callahan KS. Effect of tumor necrosis factor-alpha and interleukin-1 alpha on heme oxygenase-1 expression in human endothelial cells. *American Journal of Physiology*, 1998; 274(3 Pt 2):H883-91.

[245] Sandoval M, Charbonnet RM, Okuhama NN, Roberts J, Krenova Z, Trentacosti AM, Miller MJ. Cat's claw inhibits TNF-alpha production and scavenges free radicals: role in cytoprotection. *Free Radical Biology in Medicine*, 2000; 29(1): 71-8.

[246] Wei H, Sun R, Xiao W, Feng J, Zhen C, Xu X, Tian Z. Traditional Chinese medicine Astragalus reverses predominance of Th2 cytokines and their up-stream transcript factors in lung cancer patients. *Oncology Reports*, 2003; 10(5): 1507-12.

[247] Fernandes AC, Cromarty AD, Albrecht C, van Rensburg CE. The antioxidant potential of *Sutherlandia frutescens*. *Journal of Ethnopharmacology*, 2004; 95(1): 1-5.

[248] Obminiska-Mrukowicz B, Szczypka M. Effect of calf thymus extract and zinc supplementation on the cellular response of mice exposed to restraint stress. *Polish Journal of Vetetinary Science*, 2005; 8(1): 1-9.

6. CHANGES TO DIETARY AND LIFESTYLE REGIMENS PRIOR TO AND DURING A PANDEMIC

The proposed social distancing measures, restrictions on trade and travel, reduced workforce and likely high rates of morbidity will inevitably have considerable impacts on dietary patterns and lifestyle during a HPAI pandemic.

Fresh fruit, vegetables, meats and other foods will most likely be consumed less often, in lower quantities, with populations being much more dependent than usual on dried and canned foods. There may be challenges in the continued provision of potable water, so complications associated with dehydration may become more common.

Home-working, travel restrictions and sickness will also impact on physical activity and exercise. An observational study (n = 547) demonstrated that moderate physical activity resulted in immuno-suppression leading to a 20% reduction in the frequency of upper respiratory tract infections compared with a physically inactive population group.[249] Conversely, habitual exercise at an intense level can cause suppression of mucosal immune parameters[250] although there is evidence that immune responses can be restored by supplementation of nutrients, such as vitamin C.[251]

Psycho-social stress (associated with a pandemic) will further compromise immune function[252] and will require higher than usual nutrient intakes to compensate for increased utilization.[253,254]

Interestingly, social support, which could be enhanced among certain, well prepared population groups during a pandemic, might actually increase the effectiveness of anti-viral responses by the immune system.[255]

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[249] Matthews CE, Ockene IS, Freedson PS, Rosal MC, Merriam PA, Hebert JR. Moderate to vigorous physical activity and risk of upper-respiratory tract infection. *Medicine & Science in Sports & Exercise*, 2002; 34(8): 1242-8.

[250] M. Gleeson. Mucosal Immunity and Respiratory Illness in Elite Athletes. *International Journal of Sports Medicine*, 2000; 21: 33-43.

[251] Nieman DC, Peters EM, Henson DA, Nevines EI, Thompson MM. Influence of vitamin C supplementation on cytokine changes following an ultramarathon. *Journal of Interferon & Cytokine Research*, 2000; 20(11): 1029-35.

[252] Ader R, Cohen N, Felten D. Psychoneuroimmunology: interactions between the nervous system and the immune system. *Lancet*, 1995; 345(8942): 99-103. Review.

[253] Halliwell B, Gutteridge JMC. Role of free radicals and catalytic metal ions in human disease: an overview. In: *Methods of Enzymology*. Vol. 186. Oxygen Radicals in Biological Systems. Part 1B. *Oxygen Radicals and Antioxidants*. 1990. Academic Press, San Diego, CA.

[254] Bendich A. Physiological role of antioxidants in the immune system. *Journal of Dairy Science*, 1993; 76(9): 2789-94. Review.

[255] Miyazaki T, Ishikawa T, Nakata A, Sakurai T, Miki A, Fujita O, Kobayashi F, Haratani T, Iimori H, Sakami S, Fujioka Y, Kawamura N. Association between perceived social support and Th1 dominance. *Biological Psychology*, 2005; 70(1): 30-7.

This Expert Committee argues that it is imperative that self-care dietary and lifestyle guidelines be created and disseminated as a matter of urgency to help support the body and immune response both prior to and during an HPAI pandemic scenario.

These guidelines should include recommendations relating to:

- Social distancing measures
- Hygiene measures
- Cessation of smoking and minimisation of alcohol consumption
- Consumption of ample fresh fruit and vegetables while taking into account social-distancing measures. Home delivery of groceries, farm gate purchases or kitchen gardening are possible options
- Consumption of dried and canned foods (including oily fish[256] and/or fish oils for non-vegetarians) in such ways as to balance both micronutrients and macronutrients. Consumption of oily fish will also be important
- Exercise/activity guidelines to ensure moderate activity
- Social support recommendations
- Recommendations for vitamin, mineral and phytonutrient supplementation to offset deficiencies in dietary regimens caused by the pandemic.

[256] Calder PC, Grimble RF. Polyunsaturated fatty acids, inflammation and immunity. *European Journal of Clinical Nutrition*, 2002; 56 Suppl 3: S14-9. Review.

7. CONCLUSIONS AND RECOMMENDATIONS

7.1 CONCLUSIONS

This report has aimed to review the evidence-base for a range of key nutritional and non-pharmaceutical substances that show considerable potential for mitigation of morbidity and mortality in the event of a highly pathogenic avian influenza H5N1 viral pandemic.

The report has focused primarily on three nutrients, namely zinc, vitamin C and vitamin A, given the relatively more robust evidence for potential benefits of interventions involving these nutrients as compared with some of the other substances considered. Supporting evidence for the use several other micronutrients is also provided.

To some degree it is difficult to directly compare the effects of nutrients such as vitamins or metallo-ions as against botanical products, owing to the large variations that are typically found among the different formulations or preparations of botanically-derived products. Although some of the botanical, micro-organism or animal derived products might appear promising in relation to their potential response to H5N1 infection, standardising products to both maintain efficacy while escalating to large scale manufacture, as required in a pandemic, present major challenges.

It is highly likely that benefit could be conferred by the use of different nutritional or botanical products in combination i.e. synergistic interactions are well known for the combined use of nutrients such as vitamins A, C and E, and for example, for vitamin C and Echinacea, in relation to ailments such as the common cold. However, owing to the hyper-induction of cytokines and chemokines by HPAI H5N1, any natural product that stimulates particular cytokines such as TNF-alpha or IL-6 needs to be viewed with caution and should be subject to specific study, at least *in vitro*, to assess responses to H5N1. Studies on interactions both between nutrients and possibly even as adjuncts to specific vaccine or anti-viral medication use should be prioritized by global and national health authorities.

It is the opinion of the ANH Avian Influenza Expert Committee that interventions involving natural substances such as those considered in this report provide very potent means for mitigating negative health effects from the HPAI H5N1 virus in humans. It is clear that specific research both on individual substances and on interactions between substances would be of value to fine tune protocols and dosages both for prophylaxis and treatment (see Recommendations, Section 7.4).

In considering interventions with nutrients or other natural substances it is of paramount importance to separate those beneficial effects that are derived from relatively low-dosage interventions that aim to address nutritional deficiencies in the diet as compared with high-dosage, therapeutic interventions which seek to treat disease. The latter approach is likely to be of particular importance in treatment of people presenting with avian influenza infection. In contrast, lower dosage interventions that address the 'nutritional gap' and optimally modulate the immune system may be more appropriate for prophylaxis.

It is important to recognise some intrinsic benefits involved in using nutritional rather than anti-viral drug-based approaches. Key advantages include:

- The relatively greater ability to rapidly scale-up supply of nutrients, compared with drugs or vaccines
- The absence of serious side-effects associated with nutrients
- The very low likelihood of development of viral resistance to nutrients
- The relatively low cost of nutrients compared with drugs or vaccines
- The ability for members of the general public to engage in prophylactic intake and self-treatment in the case of nutrients which they could, in many cases, easily obtain in advance and which would typically not require prescription
- Public confidence and reassurance, based on the knowledge that natural products were readily available and that these would go a long way to reducing risk in the event of a pandemic. This would help significantly reduce anxiety or panic which might ensue if the only perceived methods of protection were based on access to anti-viral drugs or vaccines.
- The ability to reduce visits to General Practitioners, health clinics and hospitals since members of the public could source natural products by mail order, which in turn supports social distancing, travel reduction and home-working measures that are significant components of preparedness plans.

One of the greatest negative social consequences of a severe influenza pandemic that has been proposed relates to social disorder, and consequent disastrous economic consequences, that may result from shortages of food, drugs or medical care. Global and national health authorities, supported by the views of a significant number of key medical opinion leaders, have promoted vaccines and anti-viral drugs as the sole interventions that could be used to counter the virus in human populations. However, as demonstrated in Section 2.2 of this report, evidence for efficacy of vaccination and anti-viral drug therapies is very limited, especially when set against the overall evidence base for nutrient-based interventions.

Furthermore, shortages and/or lack of availability of anti-viral drugs and vaccines are highly likely over the course of a severe pandemic. These interventions are likely to be subjected to rationing and restrictions where they are available, with poor nations having limited access to such interventions in any meaningful quantities. Such restrictions are in themselves likely to promote civil unrest and disorder, where distribution decisions will be seen to be unequal and unfair by the domestic populations who fail to receive them. Provision and endorsement of nutritional interventions as a major part of pandemic management offers significant health benefits in the prophylaxis and treatment of pandemic influenza, can be easily and quickly mass produced, can be rapidly available to all, and can be used to mitigate these causes of societal breakdown and civil unrest.

In the event of a severe influenza pandemic, nutrient-based therapies administered worldwide would dramatically reduce mortality and morbidity and the dismissal of such therapies by global and national health authorities may result in the unnecessary loss of tens of millions of lives. We believe that such a dismissal would come to be seen as one of the greatest acts of professional negligence in human history.

We offer the following protocols and guidelines to the WHO and other health authorities overseeing preparedness plans and interventions for the anticipated H5N1 influenza pandemic.

7.2 PROPHYLACTIC AND THERAPEUTIC RECOMMENDATIONS TO COMBAT AVIAN INFLUENZA

We provide below a specific protocol series that has been proposed and endorsed by medical doctors under the auspices of the British Society for Ecological Medicine (*www.ecomed.org.uk*). This protocol has been compiled on the basis of evidence from peer-reviewed research (much of it contained within this report) as well as clinical experience gained over several decades in dealing with a wide range of viral infections, including those causing acute respiratory illness and associated complications.

The dietary and nutritional approaches recommended herein have been demonstrated to support and enhance immune responses to a wide range of infectious agents. It is the opinion of the BSEM that on their own, they will be therapeutic against avian influenza infection and that if a vaccine becomes available and is used, the protocols will provide an improved immune response to the vaccine.

7.2.1 Ecological medicine

Ecological medicine, the discipline of medicine from which the protocols have emerged, prefers to address the underlying causes of disease rather than to suppress the symptoms with, for example, pharmaceutical drugs based on new-to-nature chemistries. Members of this society and its sister medical societies in the USA, Canada and Australia, use dietary and nutritional approaches to improve health and combat disease, and have a long and wide experience in using nutrients both to address deficiencies and for their therapeutic actions. The following protocols and guidelines are based on the combined clinical experience and published research (a significant body of which is referenced in the present report) of physicians over a 50-year period.

The dosages recommended in these protocols have been utilized or recommended by medical doctors practising in the field of clinical nutrition for decades, and are not associated with any significant or serious side effects. In our opinion, based on experience with the treatment of other viral diseases — including epidemic influenza, measles, hepatitis, poliomyelitis, viral meningitis, and HIV/AIDS — these protocols are likely to represent the most effective treatments available or proposed at the present time.

All stresses significantly increase the body's requirements for nutrients. With vitamin C, in particular, it is important to understand that for optimal immune defence, for example during a viral onslaught, bodily requirements increase massively beyond those in a healthy state. If taken orally, vitamin C is rapidly

absorbed from the gut, and only when optimum tissue levels are achieved will surplus vitamin remain in the gut, attracting water and causing loose stools or diarrhoea. The optimum dose, which should be aimed at in these circumstances (and which will vary greatly from person to person and in different clinical circumstances including the severity of infection), is therefore considered to be just below that which causes diarrhoea. This is referred to as the 'bowel tolerance dose'.

7.2.2 Protocols

In the event of infection by H5N1, the sooner the recommended therapeutic dose levels are taken, the better. A subsequent reduction in bowel tolerance indicates that the virus is being overcome, and is generally accompanied by clinical improvement. This simple, practical dose-finding procedure must be well understood as it is of paramount importance for achieving the maximum therapeutic effect as quickly as possible.

We advise the following three protocols:

Protocol 1 - Prophylaxis; this should ideally be initiated at least one month before exposure to the H5N1 virus. In the event of a pandemic, it is anticipated that the majority of the population in most countries will have around this amount of notice as a minimum prior to being at extreme risk of infection.

Protocol 2 - Self-treatment; this should be initiated at the first sign or symptom of a possible viral infection.

Protocol 3 - Medical treatment; this protocol is reserved for serious or rapidly deteriorating cases, requiring intravenous therapy.

Protocols 1 and 2 would be initiated and continued by members of the public without the need for medical involvement. The necessary nutritional supplements should be obtained by members of the public in advance and kept in readiness at their home, school and/or work-place. Protocol 3 should only be necessary if Protocols 1 and/or 2 have not been initiated in time, or in particularly vulnerable individuals.

As a general note, child dosages specified refer to children under 6 years, including infants. Older children should receive the adult dosages.

7.2.2.1 *Protocol 1 - Prophylaxis*

Nutrient	Adult (per 24 h)	Child (per 24 h)
Zinc	25 mg	10 mg
Vitamin C	3 g	1 g
Vitamin A: or Beta-carotene:	20,000 IU (6mg) 60 mg	10,000 IU (3mg) 30 mg

Notes:

1. These amounts are safe to take continuously for many months.
2. Vitamin C should be taken in several, divided doses per day (e.g. 500 mg [0.5 g] or 1000 mg [1 g] each dose). Occasionally, some people may develop loose bowels at the above dosages, and should reduce the dose accordingly.
3. Pregnant women and those who may be pregnant should use beta-carotene (or mixed carotenoids containing beta-carotene at specified dose) not vitamin A.
4. Where necessary, a single oral vitamin A dose of 1,000,000 IU for an adult, 500,000 IU for a child can be used, which will be protective for at least 6 months.

7.2.2.2 *Protocol 2 - Self-treatment*

Nutrient	Adult (per 24 h)	Child (per 24 h)
Zinc	50 mg	20 mg
Vitamin C	Starting dose: 6 g, then every 3 hours or less to bowel tolerance	Starting dose: 2 g, then every 3 hours or less to bowel tolerance
Vitamin A or Beta-carotene:	40,000 IU (12 mg) 120 mg	20,000 IU (6 mg) 60 mg

Notes:

1. These amounts are safe to take for up to one month.
2. Pregnant women and those who may be pregnant should use beta-carotene (or mixed carotenoids containing beta-carotene at specified dose) not vitamin A.
3. If a single large vitamin A dose has been given as in Protocol 1 Prophylaxis, no further vitamin A should be taken.

Vitamin C and bowel tolerance:

1. Vitamin C should be taken every 3 hours or more frequently (e.g. hourly) throughout the day, and optionally through the night (sustained-release forms of vitamin C can be helpful before bed).
2. If loose stools develop at this dose, it should be reduced gradually until the loose stools stop.
3. As long as there are no loose stools, increase each 3-hourly dose consecutively by 2 g until loose stools do occur (bowel tolerance), then continue as for 2. above.

7.2.2.3 *Protocol 3 - Medical treatment*

Nutrient	Adult (per dose)	Child (per dose)
Zinc	40 mg	20 mg
Vitamin C	Minimum: 50 g Maximum: 200 g	Minimum: 20 g Maximum: 80 g
Vitamin B12	Minimum: 20 mg Maximum: 100 mg	Minimum: 10 mg Maximum: 50 mg

Notes:

1. This regime is designed for intravenous infusion, starting at the minimum doses above, all three nutrients being delivered together.
2. Dilution of the minimum doses in less than 1000 mL of sterile water or N saline will be hyperosmolar, which may compromise access to that vein.
3. The IV line should be maintained constantly, and the nutrients infused continuously to maintain optimum plasma levels.
4. The first dose should be administered over 6 hours.
5. Thereafter the dose should be administered over every 24 hours, continuing on immediately.
6. Oral treatment should be initiated or continued if at all possible, as per Protocol 2 above, but the injected dose remains the same in either case.

Zinc:

The dose should not be increased beyond the above.

Vitamin C:

1. The maximum dose above will require dilution in 3000mL to avoid hyperosmolarity (vitamin C is the major osmolar component by far).
2. Dose should be increased if the case deteriorates.

Vitamin B12:

1. B12 treatment is directed specifically at cytokine storm, and can be increased independently of vitamin C.
2. Administration is preferable as methylcobalamin or hydroxocobalamin, but cyanocobalamin is otherwise acceptable.

Each of these nutrients will be beneficial on its own, and if not all are available, those that are should still be administered.

7.2.3 Diet and lifestyle

7.2.3.1 *Diet*

We strongly recommend the adherence to good dietary principles for everyone, in order to support the immune system and protect against viral onslaught. To build up optimum protection, it would be important for people to have been following such dietary principles for 2-3 months prior to exposure to the avian influenza virus.

Some general guidelines are as follows:

- **Consume fresh, preferably certified organic whole foods as far as possible**. Well cultivated produce is more nutrient-dense and thus preferable; ideally it should be fresh to preserve nutrient content and locally sourced; organic is preferable wherever possible. Minimise intake of processed foods and food containing additives or preservatives.

- **Consume 5 to 9 portions of fresh fruit and vegetables per day**, preferably certified organic.

- **Consume good, healthy oils**, such as those sourced from plant sources (e.g. olive, flax) and oily fish. Avoid saturated fats and any trans fats.

- **Minimise consumption of sugar**, including hidden sugars in processed foods

- **Minimise consumption of alcoholic beverages**, to reduce stress on the body.

- **Consume at least 2-3 litres of water daily**, to maintain proper hydration of the body.

In addition to this, a good quality, multivitamin and mineral supplement containing bio-available (e.g. food-form) vitamins and minerals is regarded as essential, owing to the difficulty of obtaining optimum levels of some micronutrients from the diet alone, even in the case of so-called healthy diets. In developing countries, where this would not be feasible country-wide, dietary principles are of paramount importance. Humanitarian programmes could nevertheless be created to supply micronutrient supplements or fortified foods in addition to food and medications.

7.2.3.2 *Lifestyle*

For optimal immune function, it is been demonstrated that the following lifestyle guidelines should be followed as far as possible:

- **Cease smoking** to protect the respiratory system and reduce stress on the body

- **Minimise psychological stress** (cultivate a positive attitude in all situations, as far as possible)

- **Be moderately active** (both intense exercise and physical inactivity may suppress the immune system)
- **Sleep adequately**
- **Provide social support** to others as far as possible, while adhering to guidance from health authorities on minimising risk of H5N1 transmission.

7.3 PROTOCOL AND GUIDELINE CONCLUSION

This Expert Committee views the above BSEM protocols and guidelines, developed both from the existing scientific evidence-base, as well as from decades of clinical experience, as the state-of-the art in nutritional therapies for the anticipated avian influenza pandemic. Additional work is required to investigate the supporting role of other nutrients, botanicals and micro-organism-derived products, and combinations thereof.

This Expert Committee, and the BSEM itself, welcome collaboration with academic and research bodies as well as health authorities to help confirm and, if necessary, refine further the protocols and guidelines.

7.4 RECOMMENDATIONS

The following recommendations are offered by the Alliance for Natural Health Avian Influenza Expert Committee:

1. Conduct human trials in cases of human infection by the H5N1 virus utilising the BSEM protocols provided in this report.

2. Prioritise scaling up of supply of nutrients specified in the BSEM protocols for global requirements during a pandemic.

3. Prioritise further scientific evaluation of the nutritional intervention protocols proposed in this report by way of *in vitro* and *in vivo* studies, refining them as appropriate with feedback from human trials (Recommendation 1).

4. Develop and disseminate scientifically substantiated advice to the general public on dietary and lifestyle strategies, as well as on other non-pharmaceutical measures, that could be employed to improve the human immune response in the face of H5N1 infection.

5. Such advice should be tailored to different socio-economic, cultural and geographic population groups catering for the specific physiological, social and economic requirements of each group.

6. Conduct research using epidemiological models and existing data and forecasts to compare efficacy between pharmaceutical and nutritional interventions.

7. Undertake an economic analysis to compare manufacturing and supply capabilities for both pharmaceutical and nutritional interventions, as well as their respective costs and benefits, to help facilitate political decision-making.

8. Prioritise research to assess the role of nutrients as adjuvants to vaccines and as synergists for anti-viral medications.

9. Re-evaluate previous risk assessments on nutrient Upper Safe Levels (and future maximum permitted levels) for individual nutrient forms and alter policies accordingly to prevent restriction of public access to beneficial dosages of nutrients.

10. Establish a committee of medical and scientific experts specialised in the nutritional and herbal medicine fields to oversee development and implementation of relevant research and clinical practice in relation to H5N1 influenza and other infectious diseases.

11. Set aside appropriate funding for the necessary research to be conducted by appropriate bodies and institutes. Unlike the pharmaceutical sector, private enterprise in the natural products sector does not have the funds required to conduct the necessary trials. Funding should therefore be allocated from budgets already set aside for pandemic avian influenza by the international community.

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