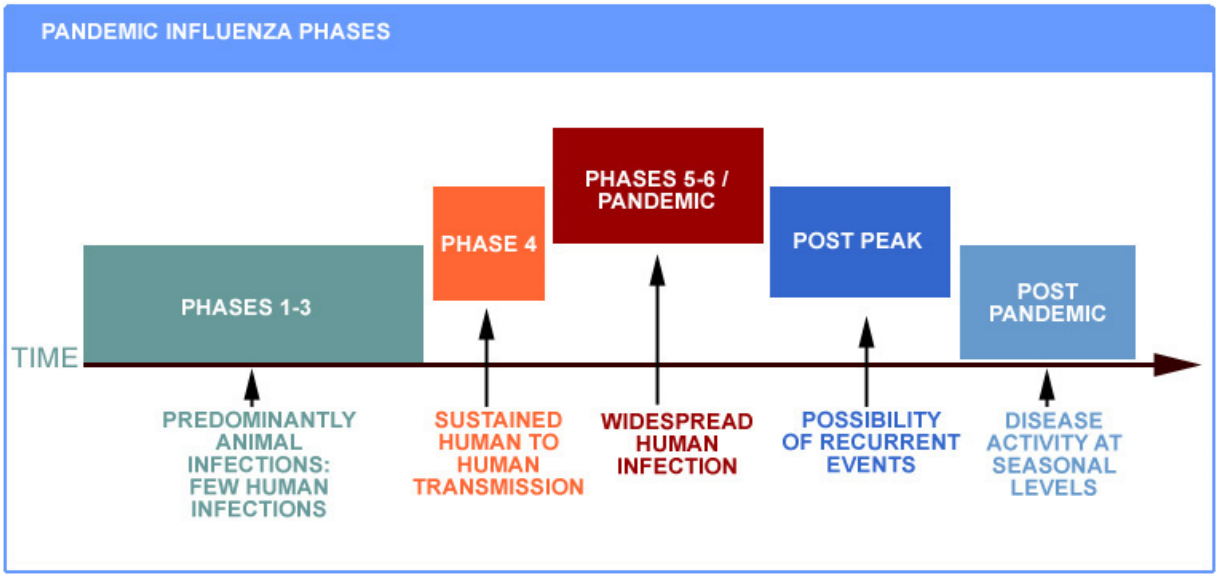
INTRODUCTION

This summary document explores the role of innate immunity and adaptive immunity in the defence and elimination of viruses. Esp. influenza. Then it explores the role of nutrients and natural agents in the optimisation of these features and looks at the evidence to support their use.



Contents

To provide a quick access to your preferred section please click on the chosen topic below.

Introduction 1
The H1N1 Swine Flu virus is a novel strain of influenza. 3
Transmissibility 3
Viruses Must First Circumvent The Mucosal Immune System. 3
Acute Viral Infection 4
What Is Being Done To Prevent Infection or Provide Treatment 4
Hygiene 4
Anti Virals 4
Oseltamivir (Tamiflu) 4
Side Effects: 5
Zanamivir (Relenza) 5
Risks: 5
Vaccination 5
Production methods: 5
Egg-allergic individuals: 5
Innate And Adaptive Immune Defence Optimisation 5
What Happens Once I Have Been Infected? 6
Boosting Immune Responses Contraindicated? 6
Can I over Stimulate immune Defence? 6
Laktoferrin: 6
Colostrum: 7
Cytokine Defence or Attack? 7
Fish Oils Contraindicated? 7
Cytokine Storms? 7
NF-kB Inhibition 8
Vitamin D: 8
Curcumin: 8
Resveratrol: 8
Green Tea Concentrates: 8
St Johns Wort: 8
Post Infection 8
Bacterial Superinfection 8
Natural Interventions For The Acute Phase Of H1N1 Infection 9
How Do We Judge The Evidence For Mucosal Immune Support 9
Disclaimer 10
References 11

A Virus is an ultramicroscopic infectious agent.

THE H1N1 SWINE FLU VIRUS IS A NOVEL STRAIN OF INFLUENZA.

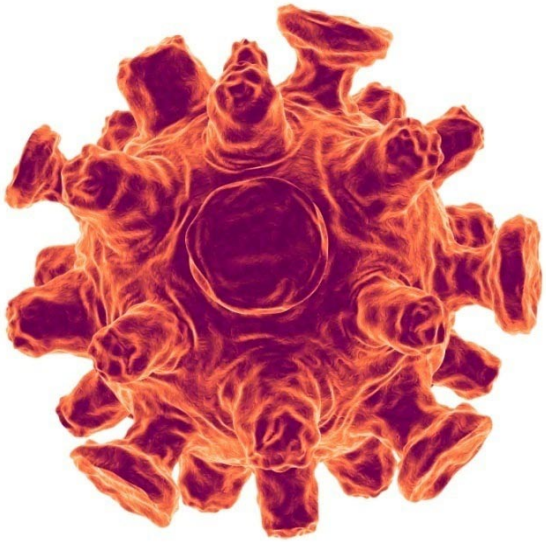
Viruses cannot reproduce in isolation. To reproduce, a virus must bind to a living cell inside some organism, insert its genetic material into that "host" cell, and take over the cell's reproductive "machinery." The virus then makes copies of itself - maybe thousands. (Sooner or later, this kills the infected cell - promoting the virus to leave the cell and cause illness). Once out of the host cell new viruses start the process over, attacking other cells until the immune system, and or medication controls their activity and replication.

TRANSMISSIBILITY

A person with swine flu and seasonal flu is at risk of spreading the virus once they are symptomatic – fever, malaise, sneezing, myalgia, gut problems etc. They are most infective with the early symptoms of sneezing, runny nose and cough. The virus replicates in the cells lining the nose and are expelled in droplets of mucous. A single sneeze can deliver 40,000 mucous droplets containing viral material.

VIRUSES MUST FIRST CIRCUMVENT THE MUCOSAL IMMUNE SYSTEM.

Mucosal immunity is important for long-term protection and forms a first line of defence against mucosally transmitted pathogens such as influenza. Mucosal defence against pathogens consists of both innate barriers, such as mucous, epithelium, and innate immune mechanisms, and adaptive host immunity. The latter consists predominantly, at mucosal surfaces, of $CD4^+$ T cells, secretory immunoglobulin A (SIgA), secretory immunoglobulin M (SIgM) and antigen-specific (memory primed) cytotoxic T-lymphocytes (CTLs).



If the infective assault on mucosal tissues is successful, by intracellular pathogens such as a virus, it will result in the induction of cell-mediated immunity. This includes the production of $CD4^+$ T helper-type 1 cells, as well as $CD8^+$ cytotoxic T-lymphocytes. These responses are normally accompanied by the synthesis of secretory immunoglobulin A (SIgA) antibodies, which provide an important first line of defence against invasion into deeper tissues by these pathogens.

Improving these first line defences through the ingestion of immune supporting nutrients presents a safe mechanism for influenza prevention. IgA and IgM, for example, can be increased via the ingestion of Saccharomyces Boulardii and Colostrum.[1]

The H1N1 Swine Flu virus is a novel strain of influenza. Existing vaccines against seasonal flu provide no protection against swine flu, and there is currently no vaccine for this strain. A study at the U.S. Centers for Disease Control and Prevention published in May 2009 found that children had no preexisting immunity to the new strain but that adults, particularly those over 60, had some degree of immunity.

Experts writing in the July 2009 New England Journal of Medicine note that "historically, pandemic viruses have evolved between seasons, and the current strain may become more severe or transmissible in the coming months." The H1N1 swine flu variant may be prone to reasortment and mutation. NEJM Influenza Centre contains further information of value.

ACUTE VIRAL INFECTION

WHAT IS BEING DONE TO PREVENT INFECTION OR PROVIDE TREATMENT

HYGIENE

Hygiene and avoidance make perfect sense. To be infected one must be exposed to a virus. Avoiding exposure and preventing inhalation or mucosal adherence via isolation and cautious care to exclude viral contaminants will prevent the development of influenza.

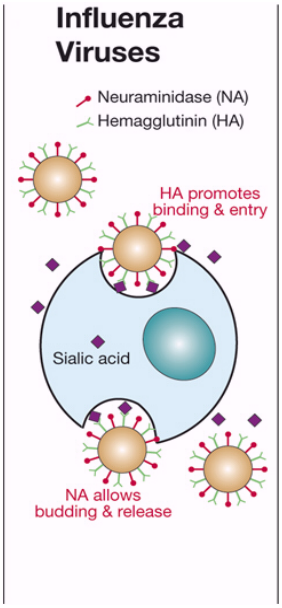
Adults of course understand this and will follow differing levels of action depending on their own personal motivation. Children are less able to manage this strategy for obvious reasons.[2]

ANTI VIRALS

Oseltamivir (Tamiflu)

Tamiflu works by inhibiting neuraminidase, a glycoprotein (*A molecule that consists of a carbohydrate (sugar) plus a protein*) on the surface of influenza virus that destroys an infected cell's receptor for viral hemagglutinin (*This protein helps virus particles bind to cells, making infection easier*). By inhibiting viral neuraminidase, this agent decreases the release of viruses from infected cells and, thus, viral spread. During this time the body's immune system will destroy the virus, the medication will not.

Neuraminidase is an enzyme which forms a spike-shaped projection on the surface of an influenza virus particle, dissolving the protective cellular mucous lining and allowing release of newly-formed virus particles from the surface of the infected cell. For Tamiflu to be effective it must be administered within 48 hours of symptom onset to provide optimal treatment. The sooner the drug is administered after symptom onset, the better the likelihood of a good outcome estimated to be a reduction in symptoms by 1-1.5 days.[3]



Two proteins on the surface of the virus enable it to enter and exit the host cell. The first protein, hemagluttinin, lets the virus attach to the cell and inject genetic material inside.

The second protein, neuraminidase, then opens the cell membrane to let the new viruses out.

Tamiflu inhibits the work of neuraminidase; that's why you hear Tamiflu called a "neuraminidase inhibitor. Hemagluttinin is the "H" and Neuraminidase is the "N" used in naming virus subtypes - like H1N1.

No one really knows what effect Tamiflu might have in terms of reducing swine flu mortality. It is rarely used in the UK. Mass use safety profiles do not exist. It may be that several million people over the coming months are given it and there may be problems with morbidity and even mortality due to the drug.

However, some studies of treatment of 'seasonal influenza' have indicated benefit, including reductions in mortality or duration of hospitalisation, even in patients in whom treatment was started more than 48 hours after illness onset. The recommended duration of treatment is 5 days.[4,5]

Antiviral treatment should be reserved for the young and under 65s during the swine flu pandemic, according to new research out on July 28th.[6] Treatment of over 65s may not lead to any significant reduction in the cumulative number of cases. The over use of Tamiflu is resulting in extra visits to GP's to manage the side effects of the medication, placing additional strain on the NHS.

Side Effects:

The most common side-effects experienced are nausea and vomiting. These symptoms generally occur within the first two days of administration of the drug. Other side-effects include diarrhea, bronchitis, abdominal pain, dizziness, headache, cough, insomnia, vertigo, fatigue.

Zanamivir (Relenza)

Zanamivir also inhibits neuraminidase. Relenza is effective against both influenza A and B. The preparation of Relenza is in powder form for inhalation.

Therapeutic Aim:

To allow the body's own immune system time to eradicate the virus, and develop immune memory. Antivirals do not stop you making immune memory cells.

Risks:

Like all medications they carry risks. However, the use of Tamiflu in children under 1 is more controversial due to a change in policy concerning the use of these drugs outside of the normal approval process, meaning normal safety data does not exist.

The use of antivirals may also increase risk for mutation of the H1N1 influenza virus that may in turn be more or less problematic.

VACCINATION

Vaccination is the process of introducing an immunogen (any substance or organism that provokes an immune response (produces immunity) when introduced into the body) consisting of a suspension of weakened or dead pathogenic cells injected in order to stimulate the production of antibodies (immunoglobulins) to produce immunity.

Influenza vaccines are produced each year as the virus mutates rapidly. However, a 2005 study questioned the benefits from influenza vaccination saying that it;

"could not correlate increasing vaccination coverage after 1980 with declining mortality rates in any age group".

This is related to seasonal flu, but may confer some accurate correlation to the yet to be developed swine flu vaccine.[7]

Production methods:

Influenza virus for vaccines are presently produced in embryonated chicken eggs. This conventional standard methodology is extremely cumbersome; it requires a huge amount of eggs (between 1-3 per dose) and an extensive purification process to reduce the amount of contaminating egg proteins and to minimise the risk of allergies against egg albumin. Influenza vaccine contains approximately 0.02-1.0 ug) egg protein.

Egg-allergic individuals:

People with an egg allergy may react to the vaccine. The ACAAI (American College of Allergy, Asthma & Immunology) recommends as a best practice that people with egg allergies be given a patch test to the flu vaccine itself.

Risks:

The introduction of the H1N1 (swine flu) vaccine will be preceded by a very short time period from production to use. It may be less able to confer protection due to mutation of the H1N1 virus. Vaccinations are not risk free.

INNATE AND ADAPTIVE IMMUNE DEFENCE OPTIMISATION

The body has a great number of natural inborn mechanisms that are effective at inhibiting the infection of influenza virus. Non specific and inducible SIgA reduces influenza virus attachment and prevents internalisation of the virus and also neutralises the virus intracellularly. The transport of polymeric IgA (pIgA is a sub form of SIgA) across epithelial cells allows active elimination of immune complexes at mucosal sites and even virus inside epithelial cells.[8] This is a well established mechanism for prevention of viral infection.[9] SIgA can be compromised by lifestyle, stress, bacterial

composition, infection, age and medication. SIgM works in tandem with SIgA to limit viral attachment and replication.

Other inducible mechanisms of innate defence include, collectins, cathelicidins, laktoferrins, lactoperoxidase, lysozyme, mucous, dendritic cells and neutrophils amongst others.

WHAT HAPPENS ONCE I HAVE BEEN INFECTED?

After initial exposure to a novel influenza viral strain, it takes between 5 and 7 days before the adaptive immune system can produce specific antibodies and T cells to arrive in the lung and gut to definitively clear the virus. This defines the time window in which innate immunity is critical. In most cases, influenza viruses remain confined to the upper respiratory tract in humans. The H1N1 virus appears to also track to gastrointestinal cells accounting for the increased gut symptoms.

Innate immune mechanisms are critical in restricting the anatomic spread of influenza virus and facilitating the rapid development of adaptive responses.

One important controversy is the extent to which some aspects of the innate response may contribute to morbidity, or even mortality, through over enthusiastic production of inflammation (commonly referred to as cytokine storms).

Boosting Immune Responses Contraindicated?

The general proposal that one may choose natural agents to 'boost' the adaptive response must be viewed with caution as specific cytokines have been linked to adverse effects and others to clinical benefits. The clinical choice should reflect current immunological understanding rather than a simple 'all boosting is good' attitude.

Overall, the optimal outcome would be that the innate response prevents dissemination of the virus without harmful inflammation and promotes effective adaptive responses that can clear the infection definitively and prevent future infections with the same viral strain (or even better, multiple viral strains).

CAN I OVER STIMULATE IMMUNE DEFENCE?

These cytokine storm related findings raise the question of whether inhibition of some aspects of the inflammatory response could have a beneficial effect in severe cases of influenza. Of particular note in this regard are reactive nitrogen intermediate (RNI) and reactive oxygen species (ROS) responses, as well as responses mediated by the special viral pathogen identifier -Toll Like Receptor -TLR3 and pro inflammatory cytokine TNF-α.[10]

TLR3 on respiratory epithelial cells plays a role in recognition of influenza viral RNA and triggering of neutrophil recruitment and other inflammatory responses.[11]

Reactive oxygen species responses are interwoven with RNI generation *in vivo*, since superoxide can react with NO to form additional reactive intermediates.

Laktoferrin plays an important antioxidant role protecting the epithelium from ROS damage by scavenging iron as free iron is a major contributor to the generation of ROS via the Fenton reaction.[12] The control of ROS is important in the management of oxidative stress in blood cells and various tissues.[13]

Laktoferrin:

Lactoferrin is a naturally occurring, nonheme, iron-binding, multifunctional glycoprotein belonging to the transferrin family and is similar to antiviral peptides, such as defensins. [14] It is produced by epithelial cells at mucosal surfaces and is secreted in milk, tears, saliva, and by neutrophils. It presents antibacterial, antiviral, and antifungal activities. [15] Laktoferrin also appears to confer its antioxidant and antiviral protection without undue suppression of natural antiviral defences.

Colostrum:

Colostrum, also a natural component of first human milk, has demonstrated effectiveness against viruses.[16]

"Immunoglobulin from bovine colostrum effectively reduces and prevents viral and bacterial infections in immune deficient subjects: bone marrow recipients, premature babies, AIDS, etc." [17]

Ingesting colostrums through the mucosal tissues of the mouth appears to confer a more pronounced respiratory immune defence. The sublingual mucosa, a readily accessible tissue, can serve as an inductive site of mucosal immune responses in the digestive, respiratory and genital tracts. The principle behind sublingual administration is as follows. When a chemical comes in contact with the mucous membrane covering the ventral part of the tongue and extending beneath the tongue to terminate at the junction with the gingiva of the inner surface of the inferior maxillary (or mandible), it diffuses into the epithelium beneath the tongue.

This region contains a high density of blood vessels and capillaries, and as a result the substance quickly diffuses through the epithelium and enters the blood stream. Such systemic responses include cell-mediated immune responses that elicit production of interferon gamma by T-lymphocyte cells.

Overall, sublingual delivery of immune support was found to be more effective than oral for inducing systemic immune responses and mucosal immune responses in the respiratory mucosa. While oral delivery is considered the most effective route for inducing a local mucosal immune response in the digestive tract.[18]

Cytokine Defence or Attack?

The production of TNF-α was found to contribute little to antiviral defence, leading to the conclusion that inhibition of TNF-α production rather than promotion might be of benefit in some cases of severe influenza virus infection as it is linked to many of the physical symptoms experienced during infection. Other proinflammatory cytokines (e.g., IL-6) have also been linked to the severity of influenza symptoms.[19]

Fish Oils Contraindicated?

The potential use of fish oils to limit the effects of activated pro-inflammatory cytokines, may well be contraindicated in H1N1 infection. Although the anti-inflammatory properties of fish oil may be beneficial during a chronic inflammatory illness, the same anti-inflammatory properties can competitively suppress the inflammatory responses necessary to combat acute viral infection, particularly IL-1.[20] This animal model suggests that 'other agents' to limit viral symptoms may be better employed than fish oil as it is has such a broad mechanism of effect rather than a targeted one.

For example; the inhibition of oxidant generation (ROS) or TLR3 activation is protective in mice infected with influenza. By contrast, prevention of IL-1 activity was not protective. IL-1 is released in the early phases of influenza infection and has potent pro-inflammatory anti viral effects. Supporting IL-1 activity may present a common pathway for improving immune defence.[21]

CYTOKINE STORMS?

The H5N1 virus (the avian flu) produced a number of fatalities linked to over expressed inflammatory cytokines. Investigations have shown that *high viral* loads correlate with an intense cytokine response, inflammation and depletion of T lymphocytes. As of yet there is no indication that Swine Flu has induced these so called cytokine storm events.

These results suggest that the inflammatory response may in fact be secondary to high viral replication and dissemination of the virus to the lungs and other sites, rather than an autonomous response that should be targeted for treatment in its own right.

Corticosteroids were tested in H5N1-infected subjects but they have not been shown to be beneficial and their use is not recommended.[22] The inhibition or limitation of viral transfer between cells appears to provide some mechanism for limitation of risk. By

optimising mucosal defence mechanisms innate immunity can achieve this effect.

As outlined earlier, some specific aspects of the innate response to influenza may be harmful and as such may provide therapeutic targets, including reduction of oxidant generation, NF-κB activation and TNF-α generation. Vitamin D has shown positive immune modulating effects in the control of IFN-γ activated macrophages, linked to respiratory distress.[23,24]

NF-KB INHIBITION

As an example, blockade of NF-κB by 'aspirin' led to a reduction of viral growth in vitro and in vivo in mice, retention of viral genetic material in the nucleus of infected cells in vitro and improved survival from lethal influenza in mice.

Caution must be displayed is considering aspirin for children under 16 as there is a risk of developing Reye's syndrome.

This suggests that the mechanism for NF-κB activation is a target for natural intervention. Many natural agents have demonstrated *NF-κB* inhibition, including; Vitamin D, flavanoids, polyphenols and curcumin.

Vitamin D:

Vitamin D has also shown excellent results in prevention of influenza infection. In North America and Europe, influenza generally reaches epidemic peaks during December–March, the months during which the sunlight and serum levels of 25-hydroxyvitamin D3 are at the lowest in the population. Although seasonal variations in temperature and relative humidity also play important roles in respiratory infections, it appears vitamin D3 can greatly reduce the risk of influenza.[25]

At least 6 studies show an inverse association between lower respiratory tract infections and 25(OH)D levels or sunshine. That is, the higher your 25(OH)D level, the fewer colds and flu.[26,27,28,29,30,31]

In the case of acute infection Dr Cannell – from the Vitamin D Council - recommends that a dose of 2000iu per kg of body weight for 7 days and then revert to prior dose.

Curcumin:

Is an effective inhibitor of NF-KB mainly through inhibition of TNF-a induced receptor inhibition.[32]

Resveratrol:

Has a role to play in managing the inflammation during the infective stage, as it preferentially inhibits TNF-α and preserves IL-1 a combination that in principle suits the mechanism of viral destruction whilst reducing the cytokine driven symptoms.[33]

Green Tea Concentrates:

Along with the hemagglutination (HA) inhibition type-specific effect, this trial also suggested that the antiviral effect of catechins on influenza virus is mediated not only by specific interaction with HA, but by altering the physical properties of viral membrane.[34]

St Johns Wort:

Has shown some IL-6 specific effects. That is Hypericum reduced levels of IL-6 in depressed patients. Whilst not a model of influenza, increased IL-6 in people infected with the influenza virus has been linked to sickness syndrome and it may offer some relief during infection when IL-6 is raised.[35]

POST INFECTION

Bacterial Superinfection

Bacterial pneumonia is a major cause of morbidity and mortality during, or shortly after, influenza epidemics and is a more common complication than viral pneumonia. Influenza virus also predisposes an individual to other infections that are introduced through the respiratory tract, such as bacterial meningitis and otitis media. There is mounting evidence that influenza alters innate immunity both early and late (e.g., up to 6 months) after infection. [36] Alterations to innate immunity account for the long-standing epidemiological observation of waves of bacterial infection following influenza epidemics. A plausible hypothesis is that the suppression of innate

response after influenza viral infection is a homeostatic response to prevent excessive inflammation in the lung environment.

These effects correlate with increased susceptibility to bacterial infection up to 6 weeks after influenza infection. Excessive production of IL-10 weeks after influenza infection has also been linked to delayed bacterial superinfection.[37]

Whilst Influenza infection induces acute type I immune response; however, 1 month after influenza infection, type II-like hypersensitivity responses are strongly potentiated.[38]

These events indicate that post infection a management course of mucosal immune support would be a judicious intervention to optimise innate mucosal immunity.

NATURAL INTERVENTIONS FOR THE ACUTE PHASE OF H1N1 INFECTION

Acute Episode	Adult & Adolescent	Child 2:7	Baby up to 2
Vit D3	2000iu per kg for 7 days from day one of positive Dx	2000iu per kg for 7 days from day one of positive Dx	400iu per kg for 7 days from day one of positive Dx
Colostrum & Laktoferrin	1000mg per day in divided doses	500-1000mg per day in divided doses	250mg mixed in food 1 x daily
Colostrum suspension	4-8 sprays under the tongue 2-5 x daily	4 sprays under the tongue 2-3 x daily	1 x sprays in the feed 2 x daily
Saccharomyces Boulardii 250mg - no GI problems	1 x 2 per day	1 per day	½ per day
Saccharomyces Boulardii 250mg - diahorrea	2 x 2 x 2 in divided doses	1 x 1 x1 in divided doses	½ x 2 per day
Green Tea	Drink infused green tea, warm or cold to remain hydrated	Drink infused green tea, warm or cold to remain hydrated	N/A
NFkB inhibitors	1-6 caps 2 x daily	1-3 caps 2 x daily	N/A

HOW DO WE JUDGE THE EVIDENCE FOR MUCOSAL IMMUNE SUPPORT

In recent years a hierarchy of the quality of evidence in medicine has been increasingly promoted, particularly for the formulation of guidelines. Hierarchies place randomised controlled trials (RCTs) at their summit, with various forms of observational studies nestling in the foothills, but information from observational studies and other foothill inhabitants (experimental investigations, analogy with similar conditions and processes, pathological, immunological, biochemical and pharmacological understanding and reasoning, and a derived assessment of risks and benefits) is also valuable.[39]

It is likely that innate host defence mechanisms play an important role in defence against novel strains associated with antigenic drift or shift. These defence mechanisms may play a greater role in more vulnerable subjects

(e.g., those who are immunocompromised in other ways).

The currently available influenza antivirals have a number of limitations. There is limited data on the use of antivirals in vulnerable populations or in severe disease. Manufacturing of the antiviral products is complex, multiple doses are often required, and there are no licensed parenteral agents. Importantly, resistance has been observed to the licensed products.

On this basis, making use of nutrients, certain strain probiotics, probiotic yeasts, and milk concentrates as a safe means of optimising innate antiviral defences is of low risk and potentially of significant benefit.

DISCLAIMER

Please note that these recommendations are based on collected data drawn from a wide range of peer reviewed journals and clinical experiences. The fact that the current H1N1 virus is novel and recent means that there are no RCT trials on the use of non pharmacological or pharmacological agents against this unique strain. There are however, certain mechanisms employed by influenza virus in the process of infection that are well known and studied. There are also well understood mechanisms of immune defence. Using these, this document has been prepared for the support of clinical decision making.

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