

The new flu pandemic - and a new way to protect ourselves.

□ Clinical immunology has largely focussed on the acquired immune system, and has generally overlooked the equally important innate immune system. A new flu pandemic may be about to strike. Unfortunately, given the delays involved in producing vaccine and current trends in anti-viral and antibiotic resistance, current public health strategies based on the above will probably be ineffective. There is an alternative strategy, based on natural compounds extracted from bakers yeast called 1-3, 1-6 beta glucans. These compounds up-regulate the innate immune system. Innate immune system up-regulation could be a critically important element in patient management and public health strategy during the pandemic - if governments everywhere take the time to study the science.

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Article

The next great flu pandemic may have arrived. A previously unseen variant of H1N1 (swine) influenza appears to have caused hundreds of illnesses and 57 deaths in Mexico, and is spreading rapidly, with new cases reported in California, Texas, New York, New Zealand, France, Spain, Israel, Canada, England and Scotland. Symptoms of the illness in Mexico include high fever, headache, eye pain, shortness of breath and extreme fatigue with rapid progression of symptoms to severe respiratory distress in about five days, with a high proportion of cases requiring mechanical respiration. Up to one in four will be affected if a pandemic broke out, and in the worst case the death toll could be as high as 2% of those infected; ie up to 1.2 million deaths in the UK. Realistically, few medical systems will be able to cope with illness and death on this scale.

History shows that flu pandemics occur at the rate of roughly three per century. There were three pandemics in the 20th century, and all spread worldwide within a year of being detected. The so-called Spanish flu in 1918-19 killed up to 50 million people. In the 50's the Asian flu pandemic killed a mere million, and in '68 Hong Kong flu killed another million or so. That was 41 years ago – so we're due for the next one. One candidate is the swine flu now gathering momentum around the world, and which has already shown cases of probable human-to-human transmission.

Antibiotics are no use in treating viral infections, and the right vaccines to protect us against the new strain of flu won't be ready until at least 6 months after the epidemic has started, which will be too late for many. Various EU member state governments

have decided to purchase anti-viral treatments for, in some cases, as many as 1 in 4 of the population. Those decisions were based on two assumptions: firstly, that the emergency could be managed, and secondly that the anti-viral drugs will be reasonably effective. Both of these assumptions are questionable. Our ability to deal with the fall-out of a contagious and highly lethal viral epidemic is, realistically, inadequate. And the efficacy of the anti-virals (which was never very high) is being under-mined by the fact that resistance to the anti-viral drugs tends to develop very rapidly. This is exacerbated by the fact that Tamiflu passes through sewage plants intact, leaching low concentrations of the drug into the waterways where wildfowl, another major flu virus host, live. This is a tried and tested way of developing drug resistance.

Let us assume, however, that the anti-viral drugs are still at least partially effective when the time comes, and the emergency plans will actually work. One in four people deemed sufficiently important (army, police, medical personnel and the political classes) will be protected. What should the rest of us do? Can nutrition really help?

Research shows that many people in hospitals and in the community suffer from sub-optimal immuno-competence, most commonly caused by Type B Malnutrition (1, 2). This has led some supplement companies to suggest the use of nutrition to support the acquired immune system as a form of protection against virulent strains of flu. In fact, this is likely to lead to increased mortality as the virulence of the most dangerous flu strains is due to their ability to trigger a cytokine storm (3), otherwise known as Systemic Inflammatory Response Syndrome or SIRS, in which an excessive immune response (specifically involving T-cells) causes so much inflammation in the respiratory tract that the victim drowns internally. Paradoxically, therefore, improved nutrition will probably increase the risk of death; and a weak immune system may be protective. This was shown by the mortality patterns in the Spanish Flu Pandemic; men and women in the prime of their lives died, while infants and the elderly were spared, in stark contrast to the trends found in most epidemics. This same worrying trend is apparent in the swine flu epidemic today.

There is, however, a role for specific immune support. A growing body of evidence shows that the best defence against viral infection may be to prepare not the acquired immune system but the less well known innate immune system, the body's first line of defence against invasion by bacteria and viruses.

Unlike the acquired (or adaptative) immune system, the innate immune system does not recognise every possible antigen. Instead, it is geared up to recognise and react to a small number of highly conserved molecules which are present in the cell walls of many pathogens; including LPS (gram negative bacteria), lipoteichoic acids (gram positive bacteria), and 1-3, 1-6 beta glucans (bacteria and fungi).

Once stimulated, the innate immune response mounts both cellular and humoral responses. These involve:

1. Phagocytic cells. These include macrophages and related cell species such as Langerhans cells in the epidermis, Kupffer cells in the liver, microglia in the brain and osteoclasts in bone.
2. Cells that produce inflammatory mediators (mast cells, eosinophils and basophils)
3. Natural Killer cells
4. Mediator molecules such as complement proteins, acute phase proteins and cytokines. These include tumor necrosis factor (TNF), interleukins 1 and 6, hydrogen peroxide and gamma interferon, all of which fight against invading pathogens.

Of all the natural compounds known to enhance innate immune system function, the best documented and most effective are the 1-3, 1-6 beta glucans, generally derived from *Saccharomyces cerevisiae* aka baker's or brewer's yeast (4, 5). These molecules activate the innate immune system very strongly indeed in humans and other mammals, and in birds, fish and crustacea (6 – 9).

Because 1-3, 1-6 beta glucans occur in the cell walls of so many bacteria and fungi, macrophages have receptors which specifically recognise these complex carbohydrates (10). When beta glucans are ingested, therefore, the innate immune system registers this as a pathogenic challenge and responds by increasing, inter alia, the number and activity of macrophages. They then increase the numbers and activity of neutrophil granulocytes, another key cell in the innate immune system. This important first line of defence is now fully activated, and several well-conducted research papers have shown that resistance to infection is greatly enhanced (4, 11, 12).

The beta glucans' ability to activate macrophages and neutrophil granulocytes has been extensively tested (10 – 13); and has been shown to protect animals such as mice against otherwise fatal infections (14, 20 - 28). Trials have shown the same substantial protective effects in human infections also (29 – 32).

A glance at the references above shows that most of the key studies had already been completed by the mid – 90's, but the work was not thought to be commercial and was not developed for clinical use. Yeast extracts were cheap, widely available, and difficult to patent – which may be why none of the drug companies was interested in investing in them.

The US army, however, was taking careful note. Starting in the late '80's, they ran an exhaustive test programme to measure the immuno-protective effects of beta glucans and over 100 other immuno-stimulants, and as recently as 2004 reported that the beta glucans were the most effective of them all. Not only did they protect against

infection with bacteria, viruses and fungi, they also conferred protection against radiation injury (33, 34).

I personally think that these valuable compounds are too good to be left to the health care professionals. As the new flu advances, I have started to give purified, high-potency beta glucans to my children, at a dose of 500 mg beta glucans per day; armed with the knowledge that they are safe (35) and effective prophylactic agents. In trials with rats, the beta glucans dramatically increased their resistance to flu infection and mortality. In trials with pigs, beta glucans reduced the harm done to the lungs after infection with swine flu virus, and reduced replication of the virus itself (36). As pigs and people have a good deal in common (metabolically and physiologically speaking), the pig model is very relevant to our own situation.

WHICH BETA GLUCAN?

There are several beta glucan preparations on the market, with greatly varying potencies. We know that beta glucans derived from yeast are far more effective than the rather different beta glucans derived from mushrooms; this is because the immune system evolved to recognise yeast infections, whereas we were never threatened by infection by mushrooms. The actual amount of beta glucan per capsule is also critical - some yeast products contain very little of the key compounds. Another criterion is purity, generally expressed as a low protein and ash content. This will minimise the risk of an allergic reaction, a potential hazard in those individuals who have an allergy to baker's yeast. As there are some very shoddy materials on the market, a reasonable option is to work with beta glucans from companies with a strong research background and an established track record.

WELLMUNE WGP (IMMIFLEX is the European version of WELLMUNE)

The beta glucan raw material with the best and most extensive R & D record is Wellmune WGP (Immiflex).

- Wellmune WGP (Immiflex) contains beta 1,3/1,6 glucans (also known as beta glucan 3-6) which is a highly purified extract from bakers yeast.
- Wellmune WGP (Immiflex) is protected by more than 40 patents and has been thoroughly tested in regards to both safety and effect, in pre-clinical and in clinical trials.
- Wellmune WGP (Immiflex) can be used continuously or taken during periods of high risk.
- Wellmune WGP (Immiflex) may be used by people with yeast allergy, since the allergy provoking compounds in the yeast (mannoproteins) have been removed.

Wellmune WGP (Immiflex) is used as an ingredient in several commercially available dietary supplements. It is made by BiotheraPharma, an US-based company which has done most of the research into these valuable compounds.

Note: the author consults with BiotheraPharma.

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A poster presentation at the International Carbohydrate Symposium in Oslo, Norway.

March 2008

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Stem Cells published online Mar 13, 2008; DOI: 10.1634/stemcells.2007-0712.

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A poster presentation at Keystone Symposia's conference on Innate Immunity: Signaling Mechanisms.

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