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Influenza prevention

Immunization and Tamiflu are not enough

by Paul Bergner

ABSTRACT

Vaccination and antiviral drugs are the standard public health measures available for pandemic influenza; these will be insufficient to provide protection for the great majority of individuals affected. Other methods of increasing host resistance may be available with dietary changes, nutritional supplementation, and herbal medicines. Research supporting the efficacy of such measures is reviewed.

Influenza pandemics occur in regular cycles, and judging from previous history, we are due for another at any time. A pandemic is a global disease outbreak that emerges when a new influenza virus emerges for which people have little or no immunity, and for which there is no vaccine. The disease can spread within populations and from country to country very rapidly.

Pandemics occurred during the 20th century in 1918, 1957, and 1968. The occurrence of a pandemic does not necessarily imply excess deaths beyond those caused by regular seasonal influenza. The 1918 Spanish flu resulted in approximately 500,000 deaths in the U.S, whereas in the 1957 Asian flu about 70,000 patients died, and in the 1968 Hong Kong flu, the number was about 33,000. Non-pandemic seasonal influenza epidemics in the U.S. cause about 36,000 deaths annually in the current era.

Once a pandemic appears, world public health agencies engage in a race to produce a vaccine to the new influenza strain before the disease is widely circulated. In the 1957 pandemic, a new strain was identified in February of that year, and the new vaccine was in production by May. It was available in limited supply by August (USHHS). The epidemic began in earnest in September, three months earlier than most seasonal outbreaks. This early seasonal appearance is typical for new strains, and may be followed by several more waves of the epidemic over the next six months. The gap between identification of the new strain and the availability of a vaccine today still may be 6-9 months or more (CDC b). Once administered, vaccines then take about two weeks to confer immunity. Millions of North Americans will be exposed to any new pandemic virus weeks to months before a vaccine is available and will need to rely on other methods to increase host resistance to the infection.

Influenza vaccines have mixed effectiveness. A vaccine well-matched to the influenza strain may prevent 80% of cases in normal healthy adults. Because of difficulty matching vaccines to the exact annual strain of influenza, and because the virus can mutate in the midst of an epidemic, typical seasonal vaccines reduce incidence in healthy adults by only about 50%. It appears that vaccines mainly prevent influenza in those who will not develop severe symptoms anyway — among healthy adults, the percentage of individuals in a vaccinated population who develop severe disease, miss days at work, or require hospitalization is the same as in an unvaccinated population, and a meta-analysis in 2004 reached the conclusion: “There is not enough evidence to decide whether routine vaccination to prevent influenza in healthy adults is effective (Demicheli; Jefferson).” Another recent meta-analysis of influenza vaccination in elders reached the conclusion that immunization does not reduce mortality in that age group (Simonsen). Simonsen and his co-authors challenged the conclusion of some studies that routine influenza immunization in nursing homes reduced overall winter mortality. Their study, published in The Lancet, found that mortality from influenza in individuals over seventy years old (who account for about 75% of all influenza mortality) remained unchanged or actually increased between the years 1980 and 2002. During that period, the percentage of elders over age seventy who were immunized rose from 15% to 65%. Vaccines may also cause major health problems in some individuals — vaccines for the Swine Flu in 1976 caused significant morbidity, and were eventually withdrawn for this reason. More than 1000 individuals were paralyzed by the vaccine before it was removed from the marketplace.

DRUG THERAPY

Influenza is treated today with two classes of drugs: adamantanes (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir/Tamiflu; and

zanamivir/Relenza). Adamantanes are only active against A strains of influenza, and not B strains. Influenza strains that are resistant to adamantane drugs emerge rapidly in epidemics where the drug is used. Up to 30% of patients treated with amantadine may shed resistant viruses, sometimes as early as day two to three after treatment. Such adamantane-resistant viruses can readily be transmitted to contacts. Most North American influenza viruses are already resistant to adamantanes. Neuraminidase inhibitors are put forth as the best treatment for those infected in a future pandemic. These are active against seasonal strains of either A or B influenza viruses. Trials have shown that Tamiflu reduces the severity of influenza in these cases, but the drug must be given early in the course of infection (within 48-60 hours). A recent review suggests that Tamiflu is much less effective for H5N1 Avian influenza (Crusat and deJong) also rapidly promotes development of viral resistance — 25% of patients in one small study (de Jong et al.) Future strains of epidemic influenza will likely become rapidly drug-resistant in any epidemic where the drug is widely used.

The most important micronutrients for immunity are zinc, vitamin A, vitamin C, vitamin E, selenium, iron, and essential fatty acids.

Vaccination and antiviral drugs are the only public health measures available for pandemic influenza, and will be insufficient to provide protection for the great majority of individuals affected. Other methods of increasing host resistance may be available with dietary changes, nutritional supplementation, and herbal medicines.

NUTRITION

General immunity is highly dependent on nutritional status; many individuals who are not overtly malnourished have micronutrient deficiencies that contribute to reduced resistance to infection. For some nutrients, their status in the system or consumption in clinical trials has been directly correlated with susceptibility to influenza infection and disease severity. Several nutrients have been demonstrated to increase the host response to influenza immunization. For an excellent review of the roles of specific nutrients in general immunity, a free full-text journal article is available through the PubMed service of the National Library of Medicine (Field et al). The most important micronutrients are zinc, vitamin A, vitamin C, vitamin E, selenium, iron, and essential fatty acids. The first five of these comprise the ZACES formula, developed in Southern Africa as a treatment for AIDS. The formula (see Table 1) is combined with a whole foods diet and other lifestyle modifications, and is now part of standard treatment for AIDS throughout Zimbabwe, South Africa and neighboring countries. The director of an AIDS treatment center in Harare, Zimbabwe, stated in an interview that the ZACES formula with lifestyle changes can "prolong the progression of HIV infection to AIDS almost indefinitely, and get the AIDS patient out of bed and back to work (James). HIV infection is clearly not influenza, but the formula apparently works by correcting any underlying deficiencies of the nutrients essential to optimal immune response, and might be useful in any viral infection.

The ZACES formula itself has not been tested in clinical trials of HIV infected individuals, but each of its components has been studied in HIV infection or AIDS, and found to be beneficial in intervention trials. This includes trials of zinc (Bobat et al; Wellinghausen et al), Vitamin A (Semba et al.2005), combinations of vitamins A,C, and E (Fawzi et al; Villamor et al.), combinations of vitamins C and E (Allard et al.), vitamin E alone (de Souza et al.), and selenium (Burbano et al; Shor-Posner et al; Kupka et al; Hurwitz et al.) Notably, each of these nutrients has also been successfully tested in intervention trials, mostly among the elderly, specifically for influenza and other respiratory infections, and to improve response to influenza vaccines. This includes a generic multivitamin (Wouters-Wesseling et al), zinc and selenium (Girodon et al), vitamin E (Hara et al), and vitamin C (Gorton et al.) See Table 2 for a description of the doses in a successful intervention trial in the elderly with a ZACES-like formula. Doses at a small fraction of those used in Africa were moderately successful in preventing respiratory infections and immunity to influenza in elders. Larger doses might be much more successful.

DEFICIENCIES IN THE POPULATION

Supplements will not necessarily increase immunity if the nutrients are not deficient in the host, but deficiencies of immunity-related nutrients are common in populations of industrialized nations. A recent study found in an Italian population of elders about 50% of the individuals were deficient in selenium, nearly 50% in zinc, and more than 20% for vitamins A and E (Ravaglia et al). A recent study in France concluded that about 70% of females were deficient in iron, and 66% deficient in vitamin C (Touvier et al). Statistics are similar in North America.

ZINC

In 2003 in Canada, the percentage of the population with inadequate zinc intake ranged from 9% of adult males aged 31 to 50 years old to 43% in male elders over the age of seventy. The figures for women were 15% of those aged 19 to 31 years and 30% of elders over seventy. (Mendelson et al) In the United States, the third National

Health and Nutrition Examination Survey found that only 50% of women over age nineteen and 50% of men over age 70 met the criteria for recommended daily intake of zinc. In the United States, only 50% of men aged 71 and over and of women aged 19 and over had adequate zinc intakes, using the Recommended Dietary Allowance as the criteria (Briefel et al). Positive responses to zinc intervention trials in the United States also suggest a widespread sub-clinical zinc deficiency in the population (Hambridge).

VITAMIN A

The prevalence of vitamin A deficiency among adults in the United States is low — about 1%. Deficiency in children is much higher, more than 30% in some groups of young children tested (Ballew et al.) Even mild vitamin A deficiency can cause a higher incidence of respiratory disease and a higher rate of mortality from infectious disease (Field).

VITAMIN C

A study by the U.S. Department of Agriculture in 1996 found that 18% of US adults consumed less than 30 mg per day of vitamin C. The recommended dietary allowance is eight times this, or 240 mg. (Hampl et al).

VITAMIN E

Gross vitamin E deficiency is rare in North America, suboptimal intake is almost universal. The National Health and Nutrition Examination Survey III in the early 1990s found that 18% of white participants, 41% of African Americans, and 28% of Mexican Americans had blood levels of vitamin E less than 20 mmol/liter, the level at which cardiovascular disease risk increases. Using the current recommendations for vitamin E intake, a 2004 survey found that more than 90% of the population fails to consume the recommended dietary intake (Ahuja et al).

SELENIUM

Optimal serum levels of selenium have not been officially established. A recent survey found an average serum level of 1.58 micro-moles/liter. Other research indicates that selenium related disease may be present at levels at or below 1.5 micromoles/L. About half the U.S. population appears to consume sub-optimal levels of selenium (Semba et al. 2007).

IRON

Iron deficiency is generally low in the U.S. population, affecting about 2-5% of males. It is much higher in females, however — nine to twenty two percent depending on age and race. Deficiencies are highest in Black and Hispanic women (CDCa). Because iron is pro-oxidant, and because excesses are readily stored in the tissues, it should not be supplemented unless a deficiency is identified by blood analysis. When deficient, effects on immunity may be profound (Field).

ESSENTIAL FATTY ACIDS

Because the Food and Nutrition Board of the National Academy of Science has not issued an official recommended daily intake of essential fatty acids, it is difficult to assess deficiencies in the population. Historical trends, however, indicate profound and deepening deficiencies in the U.S. since 1900 (Hibbein). Throughout the countries bordering the North Atlantic Ocean, seasonal consumption of cod liver oil to prevent colds and flu in winter is an established cultural phenomenon. Several intervention trials have demonstrated that cod liver oil can profoundly reduce the incidence of respiratory infections (Cannell et al). In one trial, a group of children who had experienced frequent infections in the previous year was completely infection-free during a season of taking cod liver oil. Cod liver oil provides essential fatty acids, vitamin A, and vitamin D, each of which can improve general immunity.

CHOLECALCIFEROL

Vitamin D, or cholecalciferol, is of special interest in the face of an influenza pandemic. Cholecalciferol is not actually a vitamin, but a steroid hormone with profound effects on the immune system. In human history, the primary source of this hormone has been sunlight — ultraviolet radiation acting on cholesterol in the skin produces a precursor to the hormone. Mid-day or summer exposure of the whole body (a normal exposure throughout the year in human evolution near the equator) generates the equivalent of about 10,000 IU of cholecalciferol, a level difficult to achieve with diet. Human migration out of tropical regions, and modern work and lifestyle conditions have created a situation where winter norms of serum cholecalciferol are about 20% of the levels that would be attained from tropical sunlight exposure.

Vitamin D expert John Cannell has recently published an article reviewing the specific roles of cholecalciferol in preventing influenza infections or moderating its severity (Cannell et al.) Cholecalciferol promotes immune competence specifically in the respiratory tract by assisting in the production of immune-peptides in the white blood cells there. The hormone also has anti-inflammatory effects, and specifically has a moderating influence on the production of pro-inflammatory cytokines. Part of the pathology of highly virulent influenza strains is the overproduction of such cytokines, which, in excess, may cause more damage to the system than the virus itself. Cholecalciferol may thus prevent influenza infection or moderate its severity. Supplementation with Vitamin D3 in a dose of 4000 IU per day will restore near-normal serum levels over a period of months. Higher doses to

Table 1

The ZACES formula

zinc	20 mg
beta carotene	25000 iu per day
vitamin C	2 grams twice a day
vitamin E	200 IU per day
selenium	100 mcg twice a day

Also recommended: 3-5 cloves of garlic per day, multiple vitamin containing B-complex, plus local herbs.

Note on Influenza:

double the dose if taking antibiotics,suffering from a cold, influenza, infection, or stress.

ref:SAT

Table 2

ZACES ELDERY INTERVENTION

zinc	10 mg
vitamin C	120 mg
beta-carotene	6 mg/5000 iu
alpha Tocopherol	20 iu
selenium	100 mcg

The doses here are much lower than the traditional ZACES formula, but still reduced respiratory infections. The benefits were due mainly to the minerals. C was found to be highly protective taken at onset; it reduced symptoms more than 80% compared to controls who received pain killers and decongestants.

Girodon et al.

more rapidly achieve optimal serum levels may be warranted in the face of a spreading pandemic. Although the official upper safe limit of vitamin D is 2000 IU/day, this has been revised upward by leading vitamin D researchers in the last twelve months. Hathcock et al provided evidence in January of 2007 that the safe limit should be raised to 10000 IU/day. In a study published in September 2007, researchers gave doses greatly in excess of 10000 IU/day for many months, and found no evidence of vitamin D toxicity (Kimball et al.) In order to rapidly raise serum levels toward normal, up to 40,000 IU/day might be safely given for a period of six weeks, followed by daily doses of 4000-10000 IU. Increased calcium in the serum and/or urine are the defining symptoms of vitamin D toxicity. An individual taking supplements in excess of the official upper safe limit of 2000 IU might out of prudence have serum and urine calcium measured periodically. Because vitamin D production in the skin is moderated by serum levels, Hathcock et al suggest that serum levels cannot be raised above the normal upper limit with doses of 10,000 IU/day. Except in certain uncommon genetic conditions, that dose should never produce serum levels sufficient to produce toxicity.

HERBAL MEDICINES

Taken in conjunction with nutritional support and lifestyle changes, herbal medicines may also help to prevent respiratory infections or moderate their severity. The principle of prevention in traditional herbalism is: what is good for treatment is also good for prevention, but in smaller doses.

ECHINACEA

Although echinacea species have been tested in clinical trials for their ability to prevent upper respiratory infections in general, or the common cold caused by rhinovirus in particular, they have not been tested for their ability to prevent or treat confirmed cases of influenza, a condition with a severity and a course very different from the common cold. However, the herb appears to work by increasing host anti-viral resistance, which may very well help to prevent influenza or moderate its severity if contracted.

A number of small clinical trials of echinacea for prevention of upper respiratory infections have been conducted with only mixed results. Most have had small numbers of participants, however, and when analyzed in several meta-analyses, actually show very good results for preventing colds. Combining data from fourteen previous clinical trials, one group of authors demonstrated that echinacea reduced the odds of having the common cold by 58% while taking echinacea, and the duration of colds that did occur was a day and a half shorter in the groups taking echinacea than in the groups that did not (Shah et al). The other meta-analysis demonstrated that echinacea protected against experimental infection with the rhinovirus (Shoop et al).

GARLIC

In herbal traditions throughout the world, from ancient Egypt, to China, to the folk traditions and medical herbalism of North America, garlic *(Allium sativa)* has been used to prevent or to treat respiratory infections (Bergner 2001) A number of trials have demonstrated that garlic can increase general immunity in animals or humans, and specifically strengthen components of the immune system that increase resistance to viral infection and cancer (Sumiyoshi; Bergner 1995). In a well-designed clinical trial for prevention of respiratory infections, a single capsule of a garlic product provided strong protection. The group receiving garlic had 64% fewer colds than the control group, had fewer than 30% of days sick with a respiratory infection, and duration of symp-

toms averaged 1.5 days in the garlic group compared to 5 full days among the controls (Josling).

BONESET

Boneset *(Eupatorium perfoliatum)* has been used to treat influenza and other viral respiratory infections continuously in North America since before first contact with Europeans. A review of this history was published by the Lloyd Brother pharmaceutical company in 1918 (Lloyd and Lloyd). The review describes the use of a strong boneset tincture to prevent influenza during the 1918 pandemic.

> *"Eupatorium was employed both in the course of treatment of the disease, and as a preventive. Five employees in one manufacturing establishment were afflicted in one day. At once, a prescription was filled and given to each of the large force remaining, with the direction to begin taking it immediately. None were thereafter afflicted."* (Lloyd and Lloyd)

Boneset has also been used traditionally as a topical treatment for herpes viral infection. Despite its fame, little scientific investigation of the plant has been conducted. Two trials have shown an increase in the activity of immune cells from various constituents extracted from boneset, including the water-soluble polysaccharides (Wagner et al; Wagner and Jurcic). In the latter trial, boneset polysaccharides were more potent than those of Echinacea.

AMERICAN GINSENG

Several clinical trials have found a proprietary extract of American ginseng *(Panax quinquefolium)* to be effective in preventing influenza and other respiratory infections among elders in a nursing home. In one trial, the participants took 200 mg of the preparation in a capsule a day for four months, beginning in September. Initially there was little difference in respiratory infections between the groups. By November and December, however, the frequency and duration of acute respiratory infection during the first two months of the group taking ginseng had about half the rate of respiratory infection as the placebo group. About a third of the ginseng group had infections, versus two-thirds of the placebo group. The difference in duration of symptoms was also dramatic – 5.6 days on average in the ginseng group versus 12.6 days in the placebo group (McElhaney et al 2006). None of these patients had influenza.

The same researchers had earlier tested the same ginseng protocol for its ability to prevent confirmed influenza in a nursing home (McElhaney 2004). Only one of ninety-seven patients in the ginseng group contracted influenza, compared to seven of 101 subjects in the placebo group. Data were similar for infection with respiratory syncytial virus – only one patient in the ginseng group was infected, versus 9 in the placebo group. The overall relative risk of acquiring a respiratory infection of any kind was 89% lower in the ginseng group. Significantly, about 90% of the populations being tested had received annual influenza vaccinations during the years of the trial – the ginseng greatly enhanced any effectiveness of the vaccines.

A DAILY SUPPLEMENT PROTOCOL FOR OPTIMAL IMMUNITY

Vitamin D	4,000 to 10,000 IU vitamin D3
Zinc	40 mg
Vitamin C	1000-2000 mg
Vitamin E	100-200 IU
Selenium	200 mcg
Cod Liver Oil	1 Tablespoon
Vitamin A	25,000 IU as beta-carotene
Iron.	10 mg/day, only when a diagnosed deficiency is present.

Lifestyle factors

Avoid Sleep debt

Avoid sugar and high glycemic foods.

EMPIRICAL TREATMENTS

In North American herbalism, a general application for prevention of influenza is to administer the herbs or formulas that might be used to treat it, but in lower doses. A scientific review concludes that the overall support for this method is slight, due mainly to a lack of investigation rather than to negative outcomes of trials (Guo et al.). The following empirical treatments, employed in the clinic and school community of the North American Institute of Medical Herbalism may be useful in increasing general host immunity. Although recommended doses are given, the intensity of preventive applications should depend on the degree of exposure. The busy clinician exposed frequently will naturally take a higher dose than an individual without significant contact with the sick. Higher doses may also be warranted if co-workers or family members contract influenza.

Immune tincture

Equal parts of:

Echinacea *Echinacea angustifolia*

Boneset *Eupatorium perfoliatum*

Osha *Ligusticum porteri*

Red root *Ceanothus americanus*

½ part of Licorice *Glycyrrhiza spp*.

½ part of Ginger *Zingiber off.*

The proportion of the herbs might be adjusted to match the patient, and synergist herbs other than licorice of ginger might be substituted or added.

Dose: 10-20 drops, 2-3 times a day for prevention.

Immune tincture #2

Equal parts of:

Echinacea *Echinacea angustifolia*

Oregon grape *(Mahonia spp.)*

Western red cedar *Thuja plicata*

Wild Indigo *Baptisia tinctoria*

¼ part Cayenne *Capsicum spp*

Dose: 10-20 drops, 2-3 times a day for prevention.

Elderberry syrup

Samubcol(TM) is an elderberry product widely available in health food stores. It has been successfully tested in clinical trials for influenza, but not specifically for prevention. Sambucol contains sugar or xylitol, and a more natural alternative elderberry syrup based on glycerin is available from the Herb Pharm company (Williams,OR).

Dose: 1 tsp twice a day.

Astragalus and codonopsis

These common Chinese herbs may be added to soups and stews, or brewed as teas to increase general host resistance, especially in cold weather. 1-2 sticks of each per quart of soup or tea is a good dose for prevention.

SMUDGES

Incense and smudging have been used throughout history to treat or prevent the spread of respiratory route infections. Because the influenza viral infection is normally restricted to the upper respiratory mucous membranes, smoke from medicinal incense or smudge may deliver medicinal properties directly to the tissues involved. Note that incense typically delivers four to five times the amount of particulate matter to the air as tobacco (Mannix et al). In one clinical trial in China, a traditional incense was as effective at removing bacteria from the air as conventional allopathic disinfectants (Yan et al). Common disinfectant smudges used in the community of the North American Institute of Medical Herbalism include artemisia species, salvia species, frankincense, and myrrh. One method for the practitioner, family member, or coworker who thinks they have been exposed is to take a "smudge shower." Using an appropriate smudge, close the bathroom and take off the clothes, and make the room thick with smudge. Inhale deeply, and also rub the smoke all over the surface of the body. This might be enhanced by steaming the room with a hot shower first.

SAUNA

Saunas, sweat lodges, and other methods of applying heat to the body and mucous membranes may be useful for prevention. The influenza virus normally cannot live above about 96 degrees, a condition that keeps it on the surface of the physiology, in the membranes, rather than penetrating into the hotter core. Applying hot air from without, and breathing deeply to heat the membranes, may effectively disinfect them.

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